

**NEUROBIOLOGICAL RESEARCH ON ADDICTION**  
**A Review of the Scientific, Public Health and Social Policy**  
**Implications for Australia**

**Final Report**

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**Ministerial Council on Drug Strategy – Cost Shared Funding Model project**

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## Abbreviations

AC	Adenyl Cyclase
aCG	Anterior Cingulate Gyrus
AIDS	Acquired Immune Deficiency Syndrome
ADHD	Attention Deficit Hyperactivity Disorder
ALDH	Aldehyde Dehydrogenase 2
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BBV	Blood Borne Virus
BDNF	Brain-derived Neurotrophic Factor
BLA	Basolateral Amygdala
BNST	Bed Nucleus of the Stria Terminalis
BOD	Burden of Disease
CaMkII	Calcium/calmodulin-dependent Protein-kinase II
cAMP	Cyclic AMP
CART	Cocaine and Amphetamine Regulated Transcript
CB1	Cannabinoid Receptor 1
Cdk5	Cyclin-dependent Kinase 5
CeA	Central Amygdala
COMT	Catechol-O-methyl Transferase
CPP	Conditioned Place Preference
CRF	Corticotropin Releasing Factor
D1, D2, D3, D4	Dopamine Receptors 1, 2, 3, and 4
DA	Dopamine
DAT	Dopamine Transporter
DBS	Deep Brain Stimulation
DD	Drug Discrimination
dmPFC	Dorsomedial Prefrontal Cortex
DNA	Deoxyribonucleic Acid
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Illness, 4th Edition, Text Revised
EEG	Electroencephalograph
fMRI	Functional Magnetic Resonance Imaging
FOS	Fructooligosaccharide
GABA	Gamma-aminobutyric Acid

GHB	Gamma-hydroxybutyric Acid
HIV	Human Immunodeficiency Virus
HCV	Hepatitis C Virus
HPA axis	Hypothalamic Pituitary Adrenal Axis
HRT	Hormone Replacement Therapy
ICD-10	International Classification of Disease
ICER	Incremental Cost-effectiveness Ratio
ICSS	Intracranial Self-stimulation
IDU	Injecting Drug User
LC	Locus Coeruleus
LSD	Lysergic Acid Diethylamide
LTD	Long Term Depression
LTP	Long Term Potentiation
MAOI	Monoamine Oxidase Inhibitors
MDMA	3,4-Methylenedioxy- <i>N</i> -methylamphetamine
MEG	Magnetoencephalograph
MMT	Methadone Maintenance Treatment
NAC	N-acetylcystein
NAcc	Nucleus Accumbens
NGO	Non-Government Organisations
NIDA	National Institute on Drug Abuse
NIAAA	National Institute on Alcoholism and Alcohol Abuse
NMDA	N-methyl-D-aspartic Acid
NRT	Nicotine Replacement Therapy
NPY	Neuropeptide Y
OCD	Obsessive Compulsive Disorder
6-OHDA	6-Hydroxydopamine
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PKC	Protein Kinase C
PMA	Phorbol Myristate Acetate
PTSD	Post-traumatic Stress Disorder
SPECT	Single Photon Emission Computed Tomography
SSRI	Serotonin Selective Reuptake Inhibitors
TMS	Transcranial Magnetic Stimulation

UK	United Kingdom
UN	United Nations
UROD	Ultra-rapid Opioid Detoxification
US	United States
VTA	Ventral Tegmental Area
WHO	World Health Organization

## Key Recommendations

In order to realise the promise of neuroscience and genetic research on addiction, we make the following recommendations:

- (1) Ministerial Council on Drug Strategy (MCDS) and Intergovernmental Committee on Drugs (IGCD) advocate for increased ARC and NHMRC investment in addiction neuroscience research, with a focus on increasing opportunities for:
  - Further neuroimaging and longitudinal studies
  - Collaborations between clinical and epidemiological researchers and neuroscience researchers working in each of the major fields of addiction neuroscience (animal studies, neuroimaging, genetics and translational research)
  - Research on the ethical and social implications of potential applications of addiction neuroscience
  - Translational research into the development and testing of new drug treatments suggested by addiction neuroscience research; bridging the gap between lab bench and bedside.
- (2) Developing a greater awareness of research in the clinical community, and fostering more integrated and collaborative relationships between the research and clinical communities to deliver the most clinically appropriate and effective treatments of addiction by:
  - Including addiction neuroscience research in undergraduate and postgraduate medical and other health sciences curricula
  - Funding the *Chapter of Addiction Medicine* and the *Australasian Professional Society on Alcohol and Other Drugs (APSAD)* to promote the revision of curricula
  - Forming a working group to oversee and facilitate research collaborations, such as the *Addiction Neuroscience Network Australia (ANNA)*
  - Fostering a wider public, professional and political recognition that addiction is a public health issue and that neuroscience research can make a major contribution to treating addiction more effectively by, for example, publishing a simplified version of the report suitable for the general public.



## Executive Summary

Addiction is a disorder in which individuals' control over their drug use is impaired. Individuals with an addiction continue to use alcohol, tobacco and other drugs in ways that cause significant physical, psychological or social harm to themselves or others. Over the past several decades, animal, and more recently human research, has increasingly suggested that human addictive behaviours have a genetic and neurobiological basis. These discoveries raise the potential for providing new and more effective medical treatments of addiction.

Many addiction neuroscience researchers also express the hope that an increased understanding of the neurobiological basis of addiction will lead to social policies that recognise addiction as a neuropsychiatric condition that should be treated therapeutically. This optimistic view needs to be balanced by anticipation of potential misuses and misrepresentations of this research that may impede the realisation of the potential for neuroscience and genetic research to reduce the harm associated with drug use and addiction.

This report has the following goals:

First, it aims to provide a concise and accessible summary of key findings from recent genetic and neuroscience research on addiction and of the treatment and preventive technologies that may emerge from this research.

Second, the report outlines some of the key social and ethical questions that are raised by neurobiological research on addiction, with the aim of ensuring that these technologies are translated quickly and appropriately into the treatment and prevention of addiction, and into effective public health policies towards drug use and addiction.

Third, it aims to describe existing neurobiological research on addiction in Australia with the aim of identifying ways in which the quantity and quality of this type of research can be increased.

## **Prevalence and Burden of Drug Use in Australia**

In Australia, as in most other developed countries, a significant proportion of the population are addicted to drugs. This includes: 17% of Australians who are dependent on tobacco; 8% of Australians who are dependent on alcohol; and 4-6% who are dependent on illicit drugs (such as cannabis, amphetamines and heroin).

Tobacco use is the largest contributor to the burden of disease in Australia, accounting for 7.7% of the total *Burden Of Disease (BOD)*. Most of this is attributable to nicotine dependence that results in: lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease, stroke and oesophageal cancer. Tobacco smoking is also the single largest contributor to the social costs of drug use (accounting for approximately \$31.5 billion per annum).

Alcohol abuse contributes 2.3% of the Australian BOD. In younger users, the major contributors to disease burden are accidents, injuries, and suicide attributable to the effects of intoxication. In older adults, alcohol use contributes to disease burden via alcohol dependence, liver cirrhosis, and psychosis. Alcohol use costs Australian society approximately \$15.3 billion per year.

The use of illicit drugs contributes around 2.0% of the total BOD. Dependent heroin use is the major contributor (accounting for approximately 60% of the illicit BOD). Illicit drug use costs the Australian community approximately \$3.8 billion per year.

Given the enormous health, economic and social burden arising from alcohol, tobacco, and other drug use in Australia, there is an urgent need for more effective social policies to reduce the burden of drug use and to develop more effective treatments for persons who abuse drugs or develop addictions. Neuroscience and genetic research on addiction has the potential to contribute to both goals and to thereby significantly reduce the burden of drug use and addiction.

## **What is Neurobiological Research?**

Neurobiological research is a broad, interdisciplinary field that encompasses a diverse range of scientific approaches. This is particularly true of the study of addiction which is understood to have biological, psychological and sociological

explanations. Neurobiological research encompasses studies at a number of levels of investigation. These include the study of molecular and cellular mechanisms that explain how drugs act on the brain and produce neurochemical changes within and between neurons. Neurobiology also includes studies of the genetic bases of behaviour that can predispose some to developing certain addictive behaviours, reflecting the view that genetic influences on neuropsychiatric conditions are ultimately expressed neurochemically within the brain. Neurobiology also involves the study of how these molecular and cellular mechanisms can lead to changes in the structure and function of important neural circuits in the brain that produce changes in cognition and behaviour characteristic of addiction. Finally, a significant challenge in neurobiological research is translating the results of these studies into effective treatments and public health policies in an appropriate and economical manner. The relationship between the various approaches to neurobiological research of addiction is depicted in the figure below.

There is a limit on what research can be undertaken in human subjects. Therefore, a significant proportion of neurobiological research of addiction involves the study of addictive behaviours in animals (e.g. rats, mice). Animal studies are particularly useful in investigating molecular and neuropharmacological phenomena, such as the pharmacology of addictive drugs, their molecular targets and the role of genetics. Animal models of human addiction also enable researchers to identify the neural circuitry of addiction that produce addictive cognitions and behaviours.

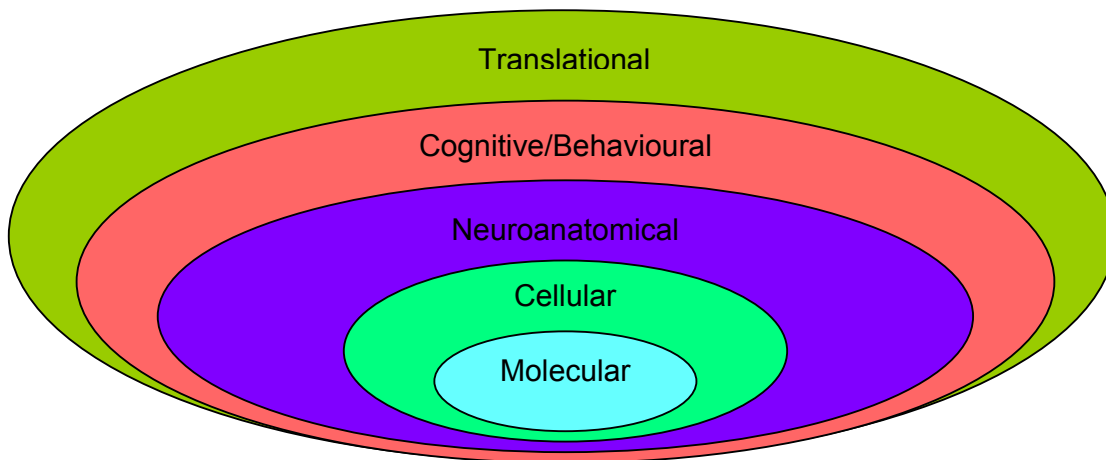
Neurobiological research of addiction in humans involves the integration of several different approaches:

1. *Human neuropathology* – the genetic, molecular and cellular study of human tissue and cell culture. The neuropharmacological and neuropathological study of addiction often involves molecular and cellular studies of post mortem neural tissues taken from addicted individuals after their deaths. These studies enable researchers to assess the effects that years of chronic drug abuse have on brain chemistry and structure.

2. *Cognitive neuroscience* – the neuropsychological study of behaviour and brain function in living humans participants. Non-invasive brain imaging techniques have enabled researchers to identify structural and functional changes in the neurochemistry and neuroanatomy of addicted individuals' brains and to study brain responses to the effects of acute and chronic drug use. Cognitive neuroscientists

also use cognitive and behavioural tasks to assess deficits or disruptions in cognition and behaviour associated with drug abuse.

3. *Psychiatric genomics* – the genomic and molecular study of behaviour in human participants. This research allows scientists to assess the role of genetics in the acquisition and development of addiction in a human population, and to identify genes and their molecular products that may be involved in the development of addiction, or that may predict response to treatment, maintenance of abstinence or susceptibility to relapse.



*molecular* - genes, neurotransmitters, intracellular signalling molecules, transporters

*cellular* - molecular trafficking, synaptic signalling, proliferation and differentiation

*neuroanatomical* - neural circuitry, functional organisation of the brain

*cognitive/behavioural* - learning, memory, executive control, emotion, motivation

*translational* – efficacy and safety, public health policy, ethics, education, resource allocation

SCHEMATIC DIAGRAM OF THE VARIOUS LEVELS OF NEUROBIOLOGICAL  
RESEARCH ON ADDICTION

## The Neurobiology of Addiction

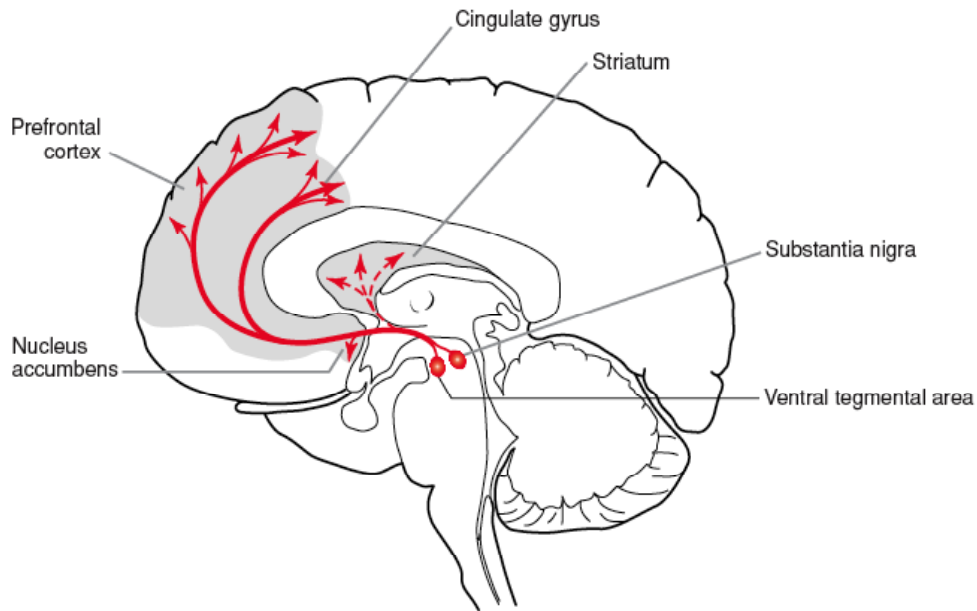
Drug addiction is characterised by the following features:

- An impaired ability to control drug use
- The development of significant physical and psychological harm arising from drug use that worsens over time
- A progressive course with repeated heavy drug use leading to the development of tolerance to the effects of drugs, withdrawal symptoms, if use is abruptly stopped, with the likelihood of relapse to drug use should an individual succeed in stopping. This pattern is often referred to as the *cycle of addiction*.

Neuroscience and genetic research on addiction are beginning to uncover the neurobiological changes in the brain that produce this pattern of addictive behaviour. Neuroscientists have shown how addictive drugs may act upon the brain's central "reward pathway" in a way that motivates some individuals to take them repeatedly, often despite the harm that they cause to themselves and others. One of the brain's major reward pathways originates in the midbrain, and projects to higher-cognitive structures of the forebrain, as depicted in the figure below. The neurotransmitter, *dopamine*, appears to be one of the central signalling molecules in this pathway. Dopaminergic neurons (neurons that release dopamine) from the *ventral tegmental area* (VTA) project to the central reward area, the *nucleus accumbens* (NAcc), and to the *prefrontal cortex*, areas primarily responsible for making decisions such as whether to use drugs or not. These are referred to as the *mesolimbic* and *mesocortical pathways*. There have been debates raised about whether dopamine is implicated in all drugs of addiction, what these increases in DA actually signify, and the role that other neurotransmitters may play in addiction.

Neuroscience research has also shown how the repeated use of addictive drugs can produce long-lasting changes in neural circuits that are involved in:

- Reward and motivation
- Affect (e.g. withdrawal)
- Learning and memory (e.g. the ability for memories to trigger relapse)
- Responses to stress
- Decision-making (e.g. the ability to inhibit impulses or urges to use drugs)



SCHEMATIC DIAGRAM OF THE BRAIN'S CENTRAL REWARD PATHWAY. DOPAMINERGIC NEURONS IN THE VTA PROJECT FROM THE MIDBRAIN TO THE NACC AND FOREBRAIN

Nearly all drugs of addiction, directly or indirectly, increase the release of dopamine into the limbic regions (e.g. nucleus accumbens, amygdala and hippocampus) and the prefrontal cortex (e.g. the anterior cingulate gyrus and orbitofrontal cortex). These regions mediate different aspects of addiction: limbic regions, such as the amygdala and hippocampus, are involved in conditioned learning in addiction, whereas the prefrontal cortex mediates emotional responses to drugs and control over drug use, such as the ability to inhibit strong urges to use drugs.

### ***Dopamine, Reward and Motivation***

Increased dopamine activity in the “reward pathway” is believed to be involved in identifying things that are desirable (e.g. food, potential mates), and learning how to ensure access to these things. The ability to identify objects or events that are rewarding, and the acquisition of behaviours that will lead to these events are cognitive abilities that are essential for survival.

The NAcc is a critical part of the neural system that is involved in learning of reward and motivation. The increase in dopamine released into the nucleus accumbens in

response to drug use signals that it is a salient event that should be repeated. Drugs of addiction act upon this natural reward pathway to motivate their repeated use.

### ***Dopamine and Withdrawal***

While drug use initially increases dopamine release, chronic drug use is thought to dramatically decrease dopamine activity. The repetitive release of dopamine is believed to lead to a dampening of activity in the reward pathway. This and other changes (see below) can produce an aversive state upon abrupt cessation of drug use that is known as *withdrawal*. This decrease can prompt a return to drug seeking in order to alleviate the symptoms of withdrawal.

### ***Other Neurotransmitter Systems Involved in Addiction***

Addiction also involves changes in a number of related neurotransmitter systems that include, but are not limited to: opioid, cannabinoid, glutamate, serotonin, and noradrenaline. Drugs that interfere with one of these neurotransmitter systems have been shown to reduce the use of a range of unrelated addictive drugs. For example, *naltrexone*, a drug which blocks the effects of opioid drugs, also reduces alcohol consumption. Similarly, *varenicline*, a drug that interferes with nicotine's brain effects appears to be useful in treating alcohol dependence, as well as nicotine dependence. While dopamine is an important signalling molecule in addiction, it is not the only neurotransmitter system involved.

### ***Conditioned-learning and Relapse to Drug Use***

The ability for events to induce craving after months of abstinence and trigger a return to drug use is a central feature of addiction. It is what makes addiction so difficult to overcome in the long-term. Long-lasting neuroadaptations in the central circuits of the brain have been hypothesized to be responsible for the induction of craving and the triggering of relapse.

Neuroscience has shown that events or stimuli associated with drug use (conditioned drug cues) can elicit craving in abstinent drug users and trigger relapse. A single exposure to a conditioned drug cue is enough to reinstate addictive behaviours in animals that have been abstinent for long periods of time. Key areas of the brain that are involved in learning also play a key role in addiction. In particular, the hippocampus and the amygdala, and the prefrontal cortex (PFC), have been shown to be critical in the acquisition, consolidation and expression of conditioned drug-cue

learning that can drive relapse to drug use. This research suggests that changes in brain functioning that lead to the formation of habits give special salience to cues related to the contexts in which drugs are used. These learned drug associations can be cues for internal states of craving that lead to relapse. Conditioned learning also involves a number of neurotransmitters in addition to dopamine, including glutamate and the orexin neuropeptides.

### ***Stress and Relapse to Drug Use***

Stress is a particularly potent trigger for relapse. Stressful events, particularly when they occur repeatedly, increase negative affect that can also induce strong drug cravings that lead to relapse. The chronic use of addictive drugs can also dysregulate the brain's stress system, producing changes in a number of stress hormones (e.g. corticotropin releasing factor). These adaptations in the stress system are thought to be the result of an attempt by the brain to maintain homeostasis in the face of chronic drug abuse. As a result of these neuroadaptations, abrupt cessation of drug use can lead to a negative emotional state. This enhances the ability of stressful stimuli to produce relapse.

Acute stress triggers the release of dopamine in the neural reward pathway that can motivate drug seeking in dependent individuals which may lead to relapse. Chronic stress can also increase vulnerability to drug use. Repeated release of stress hormones triggers dopamine release into the nucleus accumbens that can sensitise the reward system over a long period of time, and lead to a dampening of dopaminergic activity in the reward pathway in the long term. This can also lead to anhedonia – the inability to experience pleasure. This sensitisation of the reward system makes former addicts who experience stress more responsive to drugs of abuse, and therefore, more vulnerable to addiction if they use drugs.

Neuroscience research has shown that the changes associated with conditioned learning and stress can be persistent, lasting for months or more after drug use is stopped. These *neuroadaptations* leave addicted individuals vulnerable to relapse long after abstinence has been achieved. Neuroadaptations in circuits that underpin learning and memory, and responses to stress are believed to play important roles in relapse to drug use. These changes are thought to explain why certain memories, peoples and places, or stressful events trigger intense cravings for drugs that often lead to relapse months and sometimes years after stopping drug use. This, at least in



part, explains why addiction can be a chronic condition and why relapse is such a prominent feature of the disorder that makes it so difficult to treat.

### ***Deficits in Decision-making and Executive Control in Addiction***

Neuroimaging studies of human addiction have identified neurobiological changes in decision-making and executive control that are thought to explain the apparent “loss of control” and “compulsive drug” taking seen in addiction. These neural changes tend to focus the attention of addicted users on drug use, producing intense cravings for drugs, impairing appreciation of the consequences of drug use, and making it more difficult to resist urges to use drugs. These changes make the cessation of drug use difficult for a person who is addicted to that drug.

Changes in the frontal cortex of addicted individuals, particularly the *orbitofrontal cortex* (OFC) and the *anterior cingulate gyrus* (aCG), are thought to be responsible for craving and compulsive drug taking, and loss of control over drug use, respectively. The OFC provides internal representations of the saliency of events and assigns values to them, allowing individuals to compare the likely consequences of pursuing different outcomes. The aCG is involved in the inhibition of impulses to act and in the control of attention. Both of these regions appear to be dysregulated in addiction.

In addition to increased motivation to use drugs, addicted individuals often have cognitive impairments that prevent them from either recognising the consequences of their drug use or inhibiting their impulses to use drugs. Changes in the dorsolateral PFC and the aCG that seem to prevent addicted individuals from either considering options other than drug use or inhibiting their drug use. Neurocognitive tests have also found that addicted individuals have impairments in these aspects of decision-making.

There is an increasing emphasis of the role that *interoception*, the awareness of sensations of the body, plays in driving us towards choosing certain actions. Interoception is also critical in shaping or influencing the choices we make. The insular cortex has been implicated in interoception. In the case of addiction, changes to the insular cortex may play a key role in explaining why cravings have the ability to capture or steer our thinking and acting.

### ***Synaptic Plasticity and Epigenetic Changes in Addiction***

Chronic drug use leads to plastic changes in the synapses in key neural circuits that are believed to be responsible for characteristic addictive behaviours discussed previously. This process, called *synaptic plasticity*, refers to the molecular and cellular process by which information, experience or learned responses are represented in the brain by changes in the strength of neural connections. These neuroadaptations are the same molecular and cellular processes involved in the formation of memories.

These processes, known as *long term potentiation* and *long term depression*, are the basic molecular processes that occur at most synapses throughout the brain, including the mesolimbic reward pathway, and cortical regions. They are involved in strengthening or weakening synapses associated with a wide variety of cognitive functions. Drugs of abuse co-opt these synaptic plasticity mechanisms in the neural circuits involved in addiction. It is these long-lasting changes that appear to underlie the experience of drug craving, the motivation to use drugs, and relapse to drug use on re-exposure to cues associated with drug use or when put under stress.

In addition to changes at the synapse, chronic drug use also involves changes in the regulation of gene expression, referred to as *epigenetics*. Environmental events (epigenetic factors) can interfere with gene expression by physically altering the ability of transcription factors to bind to the DNA (deoxyribonucleic acid) and transcribe a given gene. Research is beginning to uncover epigenetic changes produced by drug abuse that are involved in the molecular and cellular adaptations discussed above. These mechanisms also provide another target for pharmacological intervention.

### ***Genetic and Social Vulnerability***

Addiction is a complex psychiatric disorders with a substantial heritable component. Genes may affect: behavioural traits that influence an individual's willingness to try drugs (e.g. risk-taking behaviour, impulsivity, novelty seeking); the way in which individuals respond to particular substances (e.g. drug metabolism, absorption and excretion, and activity or sensitivity to drugs); or the likelihood of developing problem use or dependence if they use drugs (e.g. by affecting how rewarding they find the effects of particular drugs or how they respond to stress). Despite the strong

evidence of genetic contributions to addiction vulnerability, attempts to reliably identify specific addiction susceptibility genes have been disappointing to date.

Neuroscience research is also beginning to provide a deeper appreciation of how social factors (such as upbringing, education, socio-economic status, and exposure to drugs, abuse or violence) can interact with an individual's genetic make-up to make them more vulnerable to developing an addiction or experiencing harms if they use drugs.

Genes and environment can have significant impacts upon brain function and behaviour, particularly during adolescence when many young people begin to experiment with drugs. Environmental stressors and early exposure to drug use, particularly during adolescence and early development, can also have significant neuropsychological effects that leave individuals vulnerable to substance abuse or addiction. These studies have provided possible explanations of why adolescents are more likely to engage in harmful drug use and are more susceptible to their detrimental effects.

## **Neurobiologically-based Treatments of Addiction**

As neurobiological research uncovers the neurochemical mechanisms associated with addictive behaviours and deficits in cognition, it raises the possibility for the following types of novel pharmacological and neurological interventions to treat addiction and reduce the harms that it causes.

### ***Pharmacological Treatments***

Neuroscience research promises to provide society with a range of pharmacological interventions. These treatments differ not only in where and how they impact on the brain, but in what part of the cycle of addiction they treat. They include:

*(1) Drugs that interfere with the action of the addictive drug on brain function:*

- *Substitution treatments* – These are drugs that mimic the action of drugs of addiction and replace the abused drug with a drug that is safer and causes less harm (e.g. methadone or buprenorphine maintenance for opioid dependence).

- *Relapse prevention* – drugs that block the effects of the drug of addiction on the brain (e.g. naltrexone for opioid dependence) thus supporting abstinence by providing a prophylaxis against relapse.
- *Detoxification* – drugs that reduce the symptoms of withdrawal and thereby make abstinence easier to achieve. This may be in the form of a *tapered withdrawal* where a substitute drug is given in decreasing doses until abstinence is achieved (e.g. methadone for opioid withdrawal). Alternatively it may involve using a drug that reduces the severity of the withdrawal symptoms (e.g. lofexidine and clonidine for opioid withdrawal).

(2) *Drugs which ameliorate changes in the dopamine system due to chronic drug use:*

- Drugs that interfere with dopamine function may reduce the cravings for drug use (e.g. antipsychotics).
- The most commonly used drug that alters dopamine signalling is bupropion (or Zyban) for the treatment of nicotine dependence.
- It is hoped that this class of drugs may provide effective treatments for psychostimulant dependence (e.g. cocaine and amphetamines) for which there are at present no effective pharmacological treatments.

(3) *Drugs that ameliorate changes in other neurotransmitter systems:*

- There are a number of other neurotransmitter systems that are disrupted by the chronic use of most addictive drugs. These include drugs that interfere with the stress (e.g. corticotropin releasing factor antagonists), opioid (e.g. naltrexone) and cannabinoid systems (e.g. rimonabant).

(4) *Drugs to reverse the persistent molecular changes at the synapse that underpin long-term changes in behaviour and cognition:*

- These include drugs that influence memory and learning at the cellular level.
- This is a new area of investigation and more research is required to determine if successful treatments of this type can be developed.

(5) *Drugs to reduce the harm caused by drug use:*

- Neuroscience may one day be able to produce drugs that mimic the action of drugs of abuse, without the physical or psychologically harmful effects. Such

drugs could include an alcohol-like drug that does not produce neurotoxic or hepatotoxic effects, or non-addictive opioid-like drugs.

### ***Novel Neurobiological Technologies***

Neuroscience research is developing a range of new medical interventions that may help to treat or reduce the harmful effects of drug use and addiction. Several of these treatments may be quite invasive or present significant safety issues that need to be evaluated before they are used more broadly. These include:

- *Vaccines* – immunological technologies that bind to a drug of addiction and prevent it from acting on the brain.
- *Depot implants* – slow release formulations of drugs such as long-acting drug implants that last for months and have the potential to reduce the problem of poor treatment compliance.
- *Neurosurgery* – Russian and Chinese neurosurgeons have destroyed parts of the brain of addicted individuals believed to be involved in addiction. This is an extremely invasive, irreversible and controversial form of “treatment”.
- *Deep brain stimulation* – a surgical procedure that involves the insertion of electrodes deep into the brain to control behaviour. It has been most often used in late-stage Parkinson’s and extreme cases of Tourette’s syndrome and obsessive-compulsive disorder. It has been suggested that this procedure may also be used to treat addiction. It carries similar, although reduced, risks to the neurosurgical procedures described above.
- *Transcranial magnetic stimulation* – a non-invasive procedure that uses magnetic fields to alter brain activity. Trials are currently underway to investigate whether this technology has a role in treating addiction.

### ***Screening and Diagnostic Technologies***

Genetic and neuroimaging technologies may be used to: 1) screen individuals for vulnerability for developing an addiction (predictive genetic screening); and 2) assist clinicians to diagnose particular deficits in addicted individuals (genetic diagnosis) and (3) identify treatments that are most likely to be effective in treating addicted individuals (pharmacogenetics). There are considerable uncertainties over the utility and validity of using genetic and neuroimaging screening to identify individuals who are more susceptible to addiction. The use of these technologies to guide treatment decisions holds more promise and is the subject of active investigation.

## **Ethical and Policy Issues in the Application of Neurobiological Research on Addiction**

New treatments for addiction derived from neurobiological research have the potential to significantly reduce the incidence and harm associated with addiction and drug use. As with any new technology, particularly those that interfere with brain function, there is also the potential for unintended harm.

Neurobiological research also has the potential to change the way in which we understand drug use and addiction, and respond to those who suffer from addiction. Neuroscience and genetic research promise to transform long running debates about whether addiction is a moral or medical problem by providing detailed causal explanations of changes in brain function in addicted individuals. For example, neuroscience research on addiction has implications for: the attribution of responsibility for addictive behaviour, the way in which addiction is treated, and the social policies used to deal with those who use drugs and continue to abuse drugs.

The medical view of addiction suggested by neurobiological research contrasts with the more punitive approaches that have dominated policies towards drug addiction for most of the last century, namely, the prosecution, detention and imprisonment of drug users and addicts. Underlying the more traditional approach is the view that compulsive drug use is a form of immoral behaviour that is best dealt with by using the criminal justice system to punish those who use illicit drugs and to deter non-users from doing so.

Some addiction neurobiologists have assumed that a neurobiological model of addiction will increase public support for less punitive ways of dealing with addiction (e.g. less imprisonment), and increase access to more effective and affordable pharmacological treatments of addiction. Critics of neurobiological models of addiction argue that they can, if misinterpreted, also lead to less benign policy outcomes. These include the neglect of social policies for reducing addiction and drug use, the adoption of more coercive policies towards addicted individuals and the use of more invasive treatments of addiction.

Addiction is a highly stigmatised condition, which causes significant harm to Australian society. Strong moral disapproval of drug use can lead to discrimination

against those with an addiction and to violations of their human rights. It could be argued, for example, that if an individual is suffering from a neurological disorder that drives them to use drugs and impairs their ability to resist urges to use them, this justifies the following policies:

- legally coerced treatment, including the coercive use of long-acting pharmacotherapies, drug vaccines, and neurosurgical technologies
- a greater reliance on medical approaches to treat addicted individuals, at the expense of social and population strategies that aim to reduce drug use or drug-related harm
- denying addicted individuals the right to consent to participate in addiction research or clinical trials of new addiction treatments
- discriminatory social policies towards vulnerable populations (e.g. prisoners, pregnant women), and
- the promotion of unevaluated diagnostic tests and treatments that are embraced by desperate and vulnerable addicted persons and their families.

Advances in genetic testing and neuroimaging that potentially enable us to identify “addicts” or to predict future risk of addiction in adolescents also raise ethical concerns that include:

- possible invasion of privacy
- the misuse by third parties (e.g. insurers and employers) of genetic and neuroimaging data
- the powers of courts to coerce defendants to undergo tests, and
- consumer protection against the misinterpretation of test results.

In order to fully realise the potential for new developments in the treatment and prevention of addiction, the Australian community needs to consider the potential ethical and social consequences of these new technologies. It also needs to discuss the impact that addiction neuroscience may have on how drug use and addiction are viewed and responded to by society. The ethical and social ramifications of this knowledge needs to be considered to ensure that the rights of those with an addiction are upheld, and a balance is found between providing effective medical care to addicted individuals while protecting Australian society from drug-related harm. Failure to do so could lead to unanticipated consequences that could affect the public’s perception and acceptance of these technologies.

Given the strong public and media interest in addiction research, neuroscientists and geneticists have a moral obligation and a professional interest in avoiding popular misunderstandings of their work. The research and development of treatments of addiction requires significant investment with limited funds, and it is critical that the financial support available is directed into areas with the greatest promise to deliver effective treatments of addiction that will be positively received by society.

## **Australian Research in Addiction Neuroscience**

Neurobiological research on addiction in Australia is a small field compared to the scale of research in the US and increasingly Europe. An audit of the impact of this Australian research indicates that it includes work of a very high international standard.

There are few Australian research groups that specialise in addiction research and most of these work on animal models of addiction. However the majority of researchers in addiction work primarily in other related fields, such as the study of other psychiatric disorders (e.g. schizophrenia) or in basic scientific research. Australia is also a world leader in post mortem studies of the brains of addicted individuals. There has been an increase in recent years in the important area of human neuroimaging research but this remains an under-developed area of addiction research in Australia, particularly by international standards. This is largely the result of the large costs in conducting neuroimaging research, limited infrastructure, and difficulty in obtaining research funding.

Neurobiological research on addiction is a highly inter-disciplinary field. Recent reviews of the field have indicated that there needs to be a greater integration of research efforts between the different types of neuroscience research. This includes animal studies, human neuroimaging and molecular genetics. While there has been some collaboration between researchers in different fields, it is still limited. This report includes suggestions on how more such research can be encouraged in Australia.



## Introduction

Over the past several decades, animal, and more recently human research has increasingly suggested that human addictive behaviours have a genetic and neurobiological basis (Volkow and Li, 2004; Nutt et al., 2007b; Schumann, 2007). Animal models of drug self-administration have enabled the brain pathways involved in the rewarding effects of drugs to be identified (Koob and Le Moal, 2006). Twin studies have identified a substantial genetic contribution to addiction to tobacco, alcohol and illicit drugs and molecular genetic studies have begun to identify individual genes that may increase **the** risk of addiction (Ball et al., 2007). Human neuroimaging studies have provided evidence that many of the same brain structures identified in animal models of addiction play a role in human addiction (Iverson et al., 2007).

Many addiction neuroscience researchers argue that this work will lead to increased funding for more effective treatments for addiction (McLellan et al., 2000; Dackis and O'Brien, 2005; Volkow and Li, 2005b). They also express the hope that an increased understanding of the neurobiological basis of addiction will lead to social policies that recognise addiction as a real neuropsychiatric condition that should be treated therapeutically (Dackis and O'Brien, 2005; Volkow and Li, 2005b). This medical view of addiction contrasts with the more punitive approaches that have dominated policies towards illicit drug addiction for most of the last century, namely, the prosecution and imprisonment of drug users and addicts. Underlying the more traditional approach is the view that compulsive drug use is simply freely chosen immoral behaviour that is best dealt with by using the criminal justice system to punish those who use illicit drugs and thereby deter others from doing so (Manski et al., 2001).

This report has the following goals. First, it aims to provide a concise and accessible summary of key findings of recent research on the genetics and neuroscience of addiction (which for purposes of brevity we will refer to as neurobiological research on addiction).

Second, it aims to describe existing neurobiological research on addiction in Australia with the aim of suggesting ways of increasing the quantity and quality of this type of

research and improving the translation of this research into effective and appropriate technologies to treat and prevent addiction.

Third, the report also outlines some of the key social and ethical questions that are raised by neurobiological research on addiction. These include the following types of questions: How may this research influence the way that modern societies think about and respond to drug use and addiction? How should we deal with the ethical issues raised by potential applications of this knowledge to treat addiction (e.g. using more targeted but expensive drugs, or coercing addicts into receiving these treatments)? How should this knowledge be used to prevent drug use and addiction? Should we, for example, try to use genetic or social characteristics to identify individuals at high risk of addiction and vaccinate them against the effects of drugs? This report does not attempt to draw conclusions on any of these contentious issues. Its aim is the more modest one of encouraging more informed public and political debate on the implications of neurobiological research on addiction in Australia.

## **Addiction and Drug Use in Australia**

Drug addiction is a pattern of behaviour in which an individual uses a drug despite the harm that their use causes, and often despite a professed desire to stop using the drug. Many addicts report finding it very difficult to stop using drugs and present for help after a series of failed attempts to quit. If they succeed in quitting, they are very likely to relapse to drug use within the period of a year in the absence of additional psychosocial and pharmacological support to remain abstinent.

Addiction is commonly understood in the two major classification systems as a disorder<sup>1</sup> in which an individual's control over their drug use is impaired. This type of definition is included in the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Illness, 4th ed. Text Revised) and ICD-10 (International Classification of Diseases, 10th ed.) diagnostic criteria for substance dependence or addiction. Both describe drug dependence as a “loss of control” over drug use, in which drug taking has become “compulsive” and consumes a great deal of an individual's time and resources, to the detriment of their performing important social roles, such as working or caring for children (World Health Organization, 1993; American Psychiatric Association, 2000).

### **Prevalence of Addiction in Australia**

In countries like Australia, the UK and the USA, a significant proportion of the population develop an addiction to alcohol (range 8-15%), tobacco (approximately 17%) and illicit drugs (range 4-6%) or both at some time in their lives (AIHW, 1999; Kessler et al., 2005; SAMSHA, 2006; McKeganey et al., 2007). In 2005-2006 there were 151,362 closed treatment episodes for alcohol and drug problems in Australia. In 96% of cases this involved a person seeking help for their own alcohol and other drug problem. Males comprised two thirds of episodes, with a median age of 31 years: 32% were aged 20 to 29 years and 10% identified themselves as of Aboriginal or Torres Strait Islander origin.

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<sup>1</sup> The term “disorder” is used to describe patterns of behaviour that commonly co-occur, are statistically uncommon and are associated with social and personal impairment.

In 2005-2006 the main substances that clients reported as prompting them to seek treatment were: alcohol (39%), cannabis (25%), opioids (17% including heroin that accounted for 14%) and amphetamines (11%). Cannabis was more often a major drug of concern among younger adults while alcohol was a more common problem among those over the age of 30 years. When taking into account the concurrent abuse of a number of substances, alcohol was a drug of concern in 54% of episodes, followed by cannabis (46%).

## Burden of Disease Attributable to Alcohol and Other Drugs

Estimates of the major contributors to burden of disease in Australia in 2003 (Table 1) indicate that tobacco smoking made the largest contribution (7.7%), followed by alcohol use (2.3%) and illicit drug use (2.0%) (Begg et al., 2007).

Drug	Males	Females	Persons
Tobacco	9.6	5.8	7.7
Alcohol (net)	3.8	0.7	2.3
Illicit drugs	2.6	1.2	2.0

TABLE 1: CONTRIBUTION (% OF TOTAL DISABILITY ADJUSTED LIFE YEARS (DALYS)) OF TOBACCO, ALCOHOL AND ILLICIT DRUGS TO BURDEN OF DISEASE IN AUSTRALIA IN 2003 (SOURCE: BEGG ET AL. (2007)).

Most of the disease burden attributable to tobacco use occurs among smokers who are nicotine dependent. Two thirds of the burden attributable to tobacco occurred in males. The major diseases contributing to this were: lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease, stroke and oesophageal cancer. Tobacco made the largest contribution to disease burden in those over the age of 60 years. The contribution climbed steeply from 40 to 70 and then declined after 80. It was higher in males than females at all ages.

The contribution of alcohol use to total Burden of Disease (BOD) was 2.3%. The harmful effects of alcohol use in younger adults (accidents and suicide) were partially

offset by the benefits of moderate consumption in reducing cardiovascular disease in older adults (Begg et al., 2007). Males accounted for 76% of total alcohol-related burden and 65% of the fatal burden. Males contributed more to alcohol burden than females at all ages, with the contribution rising steeply from the late teens and remaining high into the 80s. Much of the burden of alcohol use in younger persons arose from the effects of intoxication. In middle-aged and older adults the major contributors to disease burden are alcohol dependence and the treatment of its medical complications and deaths from liver cirrhosis and other diseases caused by chronic heavy drinking.

Heroin dependence is the major contributor to illicit drug disease burden. It accounted for 33% of DALYs (disability adjusted life years) as a primary cause and indirectly contributed to a further 30% via its role in hepatitis C virus (HCV) (23%) and hepatitis B virus (HBV) infection (7%). Cannabis use accounted for 10% of the burden attributed to illicit drugs (largely via cannabis abuse and dependence). The remaining contributors to illicit drug burden of disease were drug-related suicides (9%), benzodiazepines (5%), and 14% for other drugs. Males accounted for 71% of illicit drug related burden of disease and for the majority of all drug types except benzodiazepine (where it was only 42%). The contribution of illicit drugs to disease burden peaked in the 20-30 year age group, reflecting drug overdose deaths and suicide, before levelling off in the 40s until deaths from the complications of HCV and HBV infection began to increase in the late 40s and early 50s.

### ***The Social and Economic Costs of Drug Use in Australia***

Premature death, disease, disability and health costs do not exhaust the social costs of addiction. Addicted illicit drug users also often engage in crime and violence to finance their drug use, generating substantial law enforcement, judicial and prison costs. Illicit drug use is common among those who engage in criminal acts, with 65-80% of persons arrested in Australia having used illicit drugs prior to being arrested (Mouzos et al., 2007). Chronic use of stimulants like cocaine and methamphetamine can also produce psychoses and impulsive violence (McKetin et al., 2006). Drug abuse can lead to lost employment and increased social welfare, and broader adverse impacts on families and relationships (EMCDDA, 2006; Hall et al., 2006).

Collins and Lapsely (2007) have estimated the social costs of drug use in 2004-5 to Australian society. Tobacco smoking contributed to the largest component of social

costs (\$31.49 billion). This comprised tangible costs of \$12.03 billion (for the treatment of tobacco-related diseases and lost productivity in the workplace and the home) and intangible costs of \$19.46 billion, such as, pain and suffering and early loss of life. Alcohol accounted for \$15.32 billion. This comprised \$9.83 billion in tangible and \$4.49 billion in intangible costs. The major tangible costs of alcohol use were: crime (\$1.61 billion), road accidents (\$2.20 billion) and reduced productivity in the workplace (\$5.75 billion) and home (\$1.57 billion). Illicit drug use accounted for \$8.19 billion (\$6.95 billion in tangible and \$1.27 billion in intangible costs). The major contributions of illicit drugs to tangible costs were: crime (\$3.8 billion), production in the workplace (\$1.62 billion), road accidents (\$0.52 billion), health care \$0.2 billion), and lost production in the home (\$0.50 billion).

Given the enormous health, economic and social burden arising from alcohol and other drug abuse and addiction, there is strong public interest in preventing drug use and addiction and in helping addicts to stop using drugs or reduce drug-related harm. The policies that are often used to pursue these goals depend critically on how drug use and addiction are understood. There has been significant controversy about the nature of addiction between supporters of two dominant models. Medical models hold that addiction is a psychiatric disorder that requires treatment. In contrast more “commonsense” views that are sceptical about the existence of addictive disorders see drug use as a choice that individuals make and a behaviour for which they should be punished (e.g. if the type of drug use is illegal or if drug users engage in criminal behaviour to fund their drug use).

Neuroscience research promises to clarify our understanding of drug use and addiction. It reveals how drugs affect brain function and how chronic drug use changes the brain in ways that may make it more difficult for addicts to stop using drugs. Neuroscience research on addiction has been used, for example, to argue that addiction is a “chronic and relapsing brain disease”. The social implications of these views are very important and will be considered in some detail in this report.

# The Neurobiology of Addiction

## *The Phenomenology of Addiction*

Drug addiction or dependence<sup>2</sup> is characterised by a set of behaviours that centre around a decreasing ability to control drug use that causes physical and psychological harm (World Health Organization, 1993; American Psychiatric Association, 2000). Initial understanding of addiction was based on clinical observations of addictive behaviour. This research suggested that addiction to almost all drugs of abuse shares a number of clinical features:

1. Drug use generally begins in adolescence or early adulthood when drugs are initially taken for their positive effects on emotion, cognition or behaviour. This is referred to as **positive reinforcement**.
2. Dependent drug use follows a chronic course of initiation of use, dependency, abstinence, and relapse – commonly referred to as the **cycle of addiction** (See Figure 1.).
3. With repeated drug use individuals develop tolerance to drug effects so that greater quantities of the drug are required to achieve the same rewarding effects.
4. For most drugs of addiction, individuals will experience severe withdrawal symptoms when drug use is abruptly stopped. These symptoms are relieved by drug use and this symptom relief can be a strong motivator to continue drug use. This is referred to as **negative reinforcement**.
5. Addicted individuals continue to use the drug despite the significant physical, psychological and personal harm that its use causes.
6. Chronic drug use leads to a preoccupation with consuming the drug, subjective experiences of intense drug cravings, and a sense of a loss of control over drug use.
7. Generally, the condition progressively worsens over time, with increases in the harm caused and in subjective craving and loss of control over use.
8. Addiction is a chronic condition where most tend to relapse to harmful drug use following a period of abstinence or controlled drug use.

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<sup>2</sup> We will use the terms addiction, dependence and substance use disorders interchangeably.

## Criteria for Substance Dependence (DSM-IV)

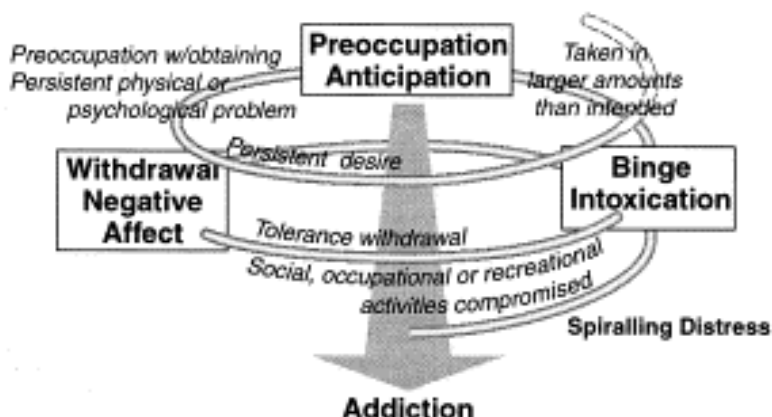


FIGURE 1. THE CYCLE OF ADDICTION. (SOURCE: KOOB AND LE MOAL (2006))

This core processes of addiction appear to be a shared by all kinds of addiction, including purely behavioural addictions, such as sex and shopping addiction, pathological eating and bulimia nervosa, and pathological gambling (Goodman, 2008). Neuroscience research is also beginning to uncover what may be a common neurobiological pathway that underlies all of these addictions (see below). People with one of these addictions are more likely than non-addicted persons to suffer from another form of addiction, or have a family member with one of these addictions (Goodman, 2008). In this report we will, however, be restricting our discussion to neurobiological research on addiction to psychoactive substances, both licit and illicit. There are a number of social and physiological differences between substance use and other addictive behaviours, notwithstanding the unique legal and regulatory situation of most psychoactive substances. For further discussion of the broader neuroscience of behavioural addictions, see Volkow and Wise (2005), Orford (2007), and Goodman (2008).

While clinical research on addiction has elucidated the aetiology and development of addiction (i.e. the cycle of addiction), the addictive behaviours that characterise it, and social factors associated with addiction (e.g. prevalence and demographic characteristics), it has yielded comparatively few effective treatments to reduce drug use. Neuroscientific studies of addictive behaviour in animal and humans are needed to understand the very specific pharmacological and anatomical changes in



brain activity that underlie the addictive process so that more effective treatments and public health policies towards drug use can be developed.

### **Neurobiological Research on Addiction**

Neuroscience of addiction employs a variety of tools and methodological approaches to understand the biology of addiction. These include: neuropharmacological studies of addictive behaviour in animal models; cellular studies of synaptic plasticity (changes in the connectivity between brain cells) using either whole organisms (*in vivo*) or animal cells or tissue (*in vitro*) models; imaging changes in brain function in human drug users and addicts; and studies of cognitive and behavioural changes in addicted humans. This research has led to a number of models or theories that attempt to explain key phenomena of addiction (e.g. incentive salience, behavioural sensitisation, associative learning, loss of executive control or behavioural inhibition, and allostasis models). A brief summary of each of these neurobiological theories of addiction is provided in Table 2. A complete review of all the theories of addiction is beyond the scope of this report. For detailed reviews of these theories, see Koob and Le Moal (2006), West (2006), and Feltenstein and See (2008).

Theories of Addiction	
<p><i>Hedonic</i> (or positive reinforcement)</p>	<p>Individuals initially use addictive substances for their pleasurable effects (or reward). Addiction develops as a result of the repeated positive reinforcing effects of addictive drugs. (Wise, 1980). Some sceptics argue that addiction does not exist: individuals simply choose to use drugs in order to experience their pleasurable effects, despite the harm that it causes (Davies, 1997; Szasz, 1975).</p>
<p><i>Withdrawal or Negative Affect</i> (or negative reinforcement)</p>	<p>Some individuals repeatedly abuse addictive drugs in order to avoid the aversive symptoms of withdrawal. Individuals initially consume addictive drugs for pleasure but repeated use leads to aversive withdrawal symptoms when use is stopped. Consequently, addicts continue to consume drugs in order to avoid these symptoms. The <i>counteradaptation hypothesis</i> and the <i>opponent-process theory</i> are forms of aversive or negative affect theories of addiction (see <i>Allostasis</i> theory below).</p>
<p><i>Self-medication</i></p>	<p>According to this hypothesis, addictive drug use begins as an attempt to reduce negative emotions, such as depression and anxiety (Khantzian, 1985, 1997). These emotions may be the result of personality or psychological deficits, or emerge in response to a stressful or abusive lifestyle. The self-medication hypothesis derived from psychodynamic theory, although is now widely embraced. The self-medication hypothesis integrates with scientific research on the role of dysregulated stress and affective</p>

	systems in addiction, but it fails to account for the very important role that chronic drug abuse plays in the production of negative affective states, such as depression and anxiety, and the sensitisation towards stressful events.
<i>Self-control or Regulation</i>	Addiction is often understood as a failure of self-regulation (Baumeister, 1994). These deficits in self-regulation may be the result of other deficits in information processing, attention, planning, reasoning, self-monitoring, and other executive control dysfunctions. Neuroscience research is now showing us that these deficits may also be caused by the deleterious effects of addictive drug abuse, as well as being a risk factor for drug use.
<b>Neurobiological Theories of Addiction</b>	
<i>Associative Learning and Habit</i>	Wise (2004) has proposed an aberrant stimulus-response learning model of addiction in which the positive reinforcing qualities of addictive drugs leads to the learning of ingrained habits. With repeated drug use, events and stimuli associated with drug use become associated with reward, or reinforcing. The presentation of these drug cues can then elicit strong emotional cravings for drug use that often lead to a relapse to chronic drug use, despite protracted abstinence (Shaham, 2005). More recent learning models of addiction have begun to elucidate the molecular and cellular mechanisms, such as long-term potentiation, synaptic plasticity and epigenetic changes, that facilitate the learning of addictive behaviours (Hyman and Malenka, 2001)
<i>Incentive Sensitisation</i>	Abused drugs produce changes in the brain's motivation and reward systems that makes these regions hypersensitive to the drug, or stimuli associated with them. Repeated use of most addictive drugs leads to increased locomotor activation, or <i>behavioural sensitisation</i> . By repeated use, stimuli associated with drug reward also become imbued with a heightened salience that increases the individual's valuing of drug use, and elicits cravings that often lead to drug use (Robinson and Berridge, 1993; Berridge and Robinson, 1995). According to this theory, the brain systems that are sensitised control the motivation to take the drug, or <i>incentive salience</i> . The sensitisation produces a shift from drug-liking to drug-wanting or craving. Incentive sensitisation is invoked to explain the development of compulsive drug taking, and the use of drugs despite the harm that they cause and in the absence of pleasurable effects.
<i>Allostasis</i>	The allostasis model of addiction expands on the <i>opponent-process theory</i> that there are opposing brain systems that attempt to maintain the system in equilibrium or homeostasis, despite significant disruptions. According to the allostasis theory, chronic use of addictive drugs produces a persistent perturbation in brain reward homeostasis. Continued drug use produces a pathological shift of the drug user's hedonic set point and a state of dysregulation of brain reward systems that results in a loss of control over drug intake and compulsive use. <i>Allostasis</i> is the process of maintaining apparent reward function stability through changes in brain reward activity (Koob and Le Moal, 2001). The allostatic state produces a chronic deviation of the reward set-point that often only becomes visible when drug use is stopped. Once drug use is stopped, the allostatic state of the reward system produces drug cravings and a return to drug-seeking. The

	allostatic state also recruits the brain's stress and negative affect pathways. The allostasis model emphasises the increasing role that neural systems involved in stress and negative affect play as addiction develops.
<i>Executive Control Dysregulation</i>	The chronic use of addictive drugs dysregulates activity in the prefrontal cortex, which produces deficits in decision-making, reduces the ability of the individual to inhibit desires to use drugs and control their behaviour (Jentsch and Taylor, 1999; Volkow, Fowler and Wang, 2003).

TABLE 2. SUMMARY OF THE MAJOR THEORIES OF ADDICTION

Addiction is a complex condition that requires genetic, molecular, cellular, neurophysiological, cognitive, psychological and social explanations. Addiction is also a dynamic process that begins with drug experimentation that may evolve into more compulsive use. Consequently, no one theory completely describes the constellation of causes and effects that characterise addiction. Theories of addiction may attempt to explain what motivates some individuals to use drugs, why some may be more vulnerable to developing an addiction should they use them, or the processes that explain why it can be difficult to stop using drugs and remain abstinent. Most recent neurobiological theories fall into this final category. Current neurobiological theories attempt to uncover the neuroadaptations, the molecular and cellular mechanisms that maintain addiction and leave addicted individuals vulnerable to relapse. Recently, attempts have begun to integrate these major theories to provide a more inclusive account of addiction.

Each of these theories provides insight into some aspects of addiction, but none provides a complete account of all aspects of addiction. While significantly increasing the breadth of our understanding of addiction, these competing models have, until recently, prevented a more unified understanding of the neurobiology of addiction. Addiction is a condition which impacts across all levels of neuroscientific analysis (e.g. molecular, cellular, and neuropsychological). In order to acquire a more accurate understanding of addiction, it is important to bring together evidence and understanding from all these very different approaches. A more complete account of the neurobiology of addiction is beginning to emerge from the convergence of findings from these different approaches to studying addiction (Koob and Le Moal, 2006; West, 2006; Goodman, 2008).

The following chapter briefly reviews neuroanatomical and neurochemical changes that appear to underlie addictive behaviour and explains how they may produce and

maintain the cycle of addiction. It concludes with a brief review of individual differences in genetic and neuropsychological make-up that can leave some individuals more vulnerable to using drugs and developing an addiction if they do so. The impact that social events can have on how these vulnerabilities are expressed is also briefly discussed.

## **The Neurocircuitry of Addiction: Insights from Animal Studies**

Animal models enable researchers to disrupt neural function (chemically, electrically or structurally) in order to understand the effects of addictive drugs on brain function in ways that would be ethically unacceptable in humans. Scientists have developed a number of sophisticated animal models for studying the neurobiology of addiction and addictive behaviours, such as: drug discrimination (DD), intracranial self-stimulation (ICSS), conditioned place preference (CPP), behavioural sensitisation and self-administration models (Balster, 1991; Colpaert, 1999; Koob and Le Moal, 2006; Feltenstein and See, 2008). A summary of the primary animal models used in addiction research are given in Table 3. These animal models have been fundamental in understanding the addictive property of drugs of abuse, investigating the acute pharmacological action of these drugs in specific regions of the brain that drive animals to repeatedly self-administer addictive drugs, and highlight changes in neurobiological pathways that are thought to trigger craving and drug seeking behaviours in human addiction. These changes are believed to be important in the persistent problem of relapse and a return to drug use after abstinence has been achieved. This early research has helped to identify the brain “reward” pathway, a central feature of neurobiological theories of addiction, and the role that the key neurotransmitter dopamine plays in signalling reward.

In recent years, the ability to genetically manipulate animals has allowed researchers to understand in greater detail the neuropharmacology of addiction and the role that certain genes may play in the development and maintenance of addiction. It has also revealed how the expression of certain genes in the brain may lead to changes in neurobiology and behaviour. It also illuminates the effects that the environment may have on the expression of these genes, and why some individuals may be genetically more vulnerable to addiction if they are subjected to certain environmental events. Animal models also serve as a powerful tool for preclinical trials and development of new drugs to treat addiction.

Animal Models of Addiction	
Drug Discrimination (DD)	Animals are trained to press one of two levers, depending on whether they receive a target drug or placebo injection. Once the discrimination is learnt, the animal will press the target lever whenever they receive the target drug or one with similar effects. Drug discrimination enables researchers to study the behavioural effects of different drugs, the neurochemical mechanisms of addictive behaviour and to discover new drugs.
Intracranial Self Stimulation (ICSS)	Animals, generally rodents, with tiny electrodes inserted into particular brain regions, will press a lever that delivers a short electrical stimulation into these regions. ICSS directly activates the neuronal circuits targeted by addictive drugs that are involved in motivation and reward. It was instrumental in elucidating the brain's reward pathway and establishing the abuse potential of addictive drugs by showing that their administration reduces ICSS thresholds: addictive drugs are reinforcing and reduce the amount of brain stimulation sought by animals. Withdrawal from addictive drugs increases ICSS thresholds. This technique can be used to monitor the hedonic state of an animal.
Conditioned Place Preference (CPP)	An animal's preference for a particular environment can be used to assess the reinforcing qualities of drugs of abuse. Animals are given an addictive drug in one of two interconnected boxes. According to classical conditioning, the animal will prefer the previously drug-paired environment. The positive reinforcing capacity of the administered drug is assessed by the amount of time spent in the drug-paired environment. CPP can also be used to assess the efficacy of pharmacological treatments of addiction. A similar method can be used to assess aversive effects of withdrawal. Animals exposed to a particular environment during withdrawal will spend less time in the withdrawal-paired environment. This is referred to as <i>conditioned place aversion</i> .
Behavioural Sensitisation	<i>Behavioural Sensitisation</i> is the progressive increase in locomotor or neurophysiological activity as a result of repeated administration of psychostimulants, alcohol and opioids. Behavioural sensitisation is hypothesised to reflect a shift from drug "liking" to drug "wanting", and thereby to mirror the development of addictive behaviours, such as compulsive drug taking, craving and relapse (see <i>Incentive Sensitisation</i> theory of addiction; Robinson and Berridge, 1993; Berridge, 2007).
Self-administration	<i>Self-administration</i> is the most widely accepted animal model of addiction. While behavioural sensitisation and CPP are useful techniques for evaluating the neurophysiological and chemical effects of repeated drug administration, they do not reflect the contingent nature of drug administration that is central to addiction. In the self-administration model, animals are trained to perform a behaviour, e.g. press a lever, in order to obtain an addictive drug. Most animals will self-administer most drugs that are addictive in humans. The self-administration model can be

	used to predict the abuse potential of new drugs, or the effectiveness of pharmacological treatments for addiction.
Extinction	<i>Extinction</i> procedures assess the persistence of motivational or reinforcing properties of drugs by measuring how long animals continue drug seeking in the absence of reward. Extinction is assessed in animals that have been trained to self-administer an addictive drug, or have developed CPP or behavioural sensitisation through repeated drug administration.
Reinstatement	A return to drug use following a period of abstinence may be triggered by the consumption of a small amount of drug ( <i>drug priming</i> ), stimuli or events associated with drug use ( <i>cue-induced relapse</i> ), or stress. Researchers use a <i>reinstatement paradigm</i> in order to model relapses to drug use in human addiction. First, animals are trained to display addictive-like behaviours (e.g. self-administration, CPP or behavioural sensitisation). Second, these are then extinguished, as per the extinction model. Third, animals are exposed to a stimuli or event, such as a small drug reward, environments in which drugs were previously given, or stress in order to trigger a return to drug use or drug-seeking behaviour (e.g. self-administration, CPP or behavioural sensitisation). This reinstatement of drug use is claimed to be a valid model of relapse. The reinstatement model has been particularly useful in elucidating the pharmacological and neurophysiological mechanisms that produce relapse. Some researchers argue that the reinstatement model also mimics other human addiction behaviours, such as craving. However, the validity of this latter claim is hotly debated (e.g. Epstein et al., 2006; Littleton, 2000).

TABLE 3. SUMMARY OF ANIMAL MODELS OF ADDICTION

Animal models of addiction enable researchers to study the molecular, cellular and neurobiological mechanisms of addiction in ways that are impossible to do in humans. While animal models do not completely emulate the addictive condition in humans, they do enable scientists to model certain aspects of human addiction, such as symptoms or behaviours characteristic of addiction (e.g. intoxication or positive reinforcement, drug seeking, and withdrawal or negative reinforcement). Recent studies have attempted to relate specific animal models to specific symptoms of the DSM-IV criteria for Drug Dependence, such as escalation in drug use or inability to control use. See Koob and Le Moal (2006) for more details.

### ***The Neurobiology of Reward, Learning and Addictive Drugs***

The ability to identify things in the environment that are rewarding or positive is a critical cognitive ability that animals and humans require for their survival. It helps to identify activities that are worth pursuing and motivates us to repeat them. The

brain's "reward pathway" was first identified in the early 1950s in animal experiments using intracranial self-stimulation (Olds and Milner, 1954). Small microelectrodes were inserted into the brains of animals, such as rats, that were electrically stimulated when an animal pressed a lever. The animals would self-stimulate at a high rate when the electrodes were placed in particular regions of the brain, that include the *ventral tegmental area* (VTA) of the midbrain and the limbic system, including the *nucleus accumbens* (NAcc), amygdala, and striatum, in the forebrain. Electrical stimulation of other regions of the brain did not produce self-stimulation. This neural circuit is referred to as the **mesolimbic reward pathway** (see Figure 2.). It is now widely understood to be the central pathway of the brain that is involved in signalling whether an activity or event is rewarding, and therefore should be repeated. Behaviours that stimulate the reward pathway, and make us want to repeat them are referred to as **reinforcers**.

Scientists have identified the neurochemical targets in the brain for all of the major drugs of addiction, which are listed in Table 4 (Koob and Le Moal, 2006). The highly diverse pharmacological profiles of addictive drugs and the types of receptors they interact with explain the wide range of physiological and behavioural changes that they produce (e.g. sedation, euphoria, hyper-arousal, hallucinations). Despite this diversity of effects, research suggests that addictive drugs may share a common reward neural circuitry. Nearly all drugs of addiction appear to activate the reward pathway by directly or indirectly stimulating the release of dopamine (DA)<sup>3</sup>: a fact that was believed to be critically important in the development of addiction (Wise, 1996; Volkow and Li, 2004). There is, however, increasing controversy in the literature whether this is true of some drugs of addiction (e.g. Daglish et al. (2008)), or what these increases in DA actually signify.<sup>4</sup> Dopamine does not explain all facets of addiction, especially to opioids. Other neurotransmitter systems are involved in the learning and reinstating of addictive behaviour and the euphoric effects of addictive drugs. We discuss these in more detail below.

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<sup>3</sup> Neither benzodiazepines nor solvents (e.g. toluene) have been shown to increase DA in the NAcc.

<sup>4</sup> In recent years, some researchers have questioned this received wisdom arguing that dopamine (with the possible exception of psychostimulant abuse) is not required for the initiation of addiction, that is the rewarding properties of addictive drugs, and is more important in the learning of reward, that is, the association drug-induced reward with specific events or cues.

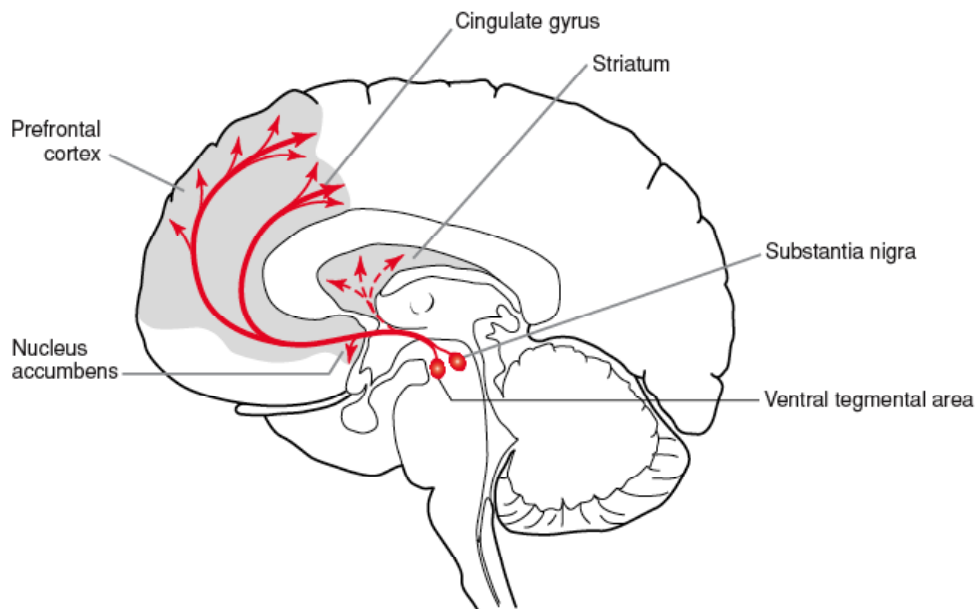


FIGURE 2. PROJECTIONS FROM THE MIDBRAIN TO THE NACC AND FOREBRAIN

Dopaminergic neurons from the ventral tegmental area (VTA) and substantia nigra, project to the central reward area, the nucleus accumbens (NAcc), and to the cortical areas primarily responsible for making decisions, such as whether to use drugs (e.g. the prefrontal cortex (PFC), and the anterior cingulate gyrus (aCG). Projections from the midbrain also make connections with the striatum (e.g. caudate and putamen) (Source: Hyman et al., 2006).

Drugs vary considerably in how they trigger dopamine release (Cami and Farre, 2003). Amphetamines, cocaine, alcohol, opioids, nicotine and cannabis (Koob and Bloom, 1988; Johnson and North, 1992; Weiss et al., 1993), directly or indirectly, act on the nucleus accumbens (NAcc) and other brain structures producing large and rapid increases in dopamine (Robbins et al., 2007). Psychostimulants, such as cocaine and amphetamines, increase the amount of dopamine available for post-synaptic signalling either by increasing dopamine release or by reducing dopamine reuptake from the synapse (Hutcheson et al., 2001). Dopamine reuptake is reduced by blocking the dopamine transporter (DAT), which increases the amount of dopamine in the synapse, and therefore increases dopamine signalling. Refer to Figure 3. Cocaine has also been shown to block both the noradrenaline and serotonin transporters (Koob and Le Moal, 2006). Alcohol, opioids, cannabis and



nicotine<sup>5</sup> increase dopamine activity indirectly, by stimulating neurons that influence dopaminergic neurons (Nisell et al., 1994; Koob and Le Moal, 1997). See Figure 4. For example, alcohol binds to gamma-aminobutyric acid (GABA) receptors that reduce the inhibitory influence of GABAergic neurons on dopamine-firing cells.

Drug	Target
Opioids	Agonist at mu, delta and kappa opioid peptide receptors
Cocaine	Inhibits dopamine transporter
Amphetamines	Stimulates dopamine release. May also stimulate noradrenaline and serotonin release depending on the precise amphetamine analogue being used.
Ethanol	Facilitates GABA-A and inhibits NMDA glutamate receptor function
Nicotine	Agonist at nicotinic acetylcholine receptors
Cannabinoids	Agonist at cannabinoid CB1 and CB2 receptors
Benzodiazepines	Facilitates GABA-A function

TABLE 4. THE NEUROCHEMICAL SITES AT WHICH DRUGS OF ADDICTION ACT (SOURCE: NUTT AND LINGFORD-HUGHES (2008)).

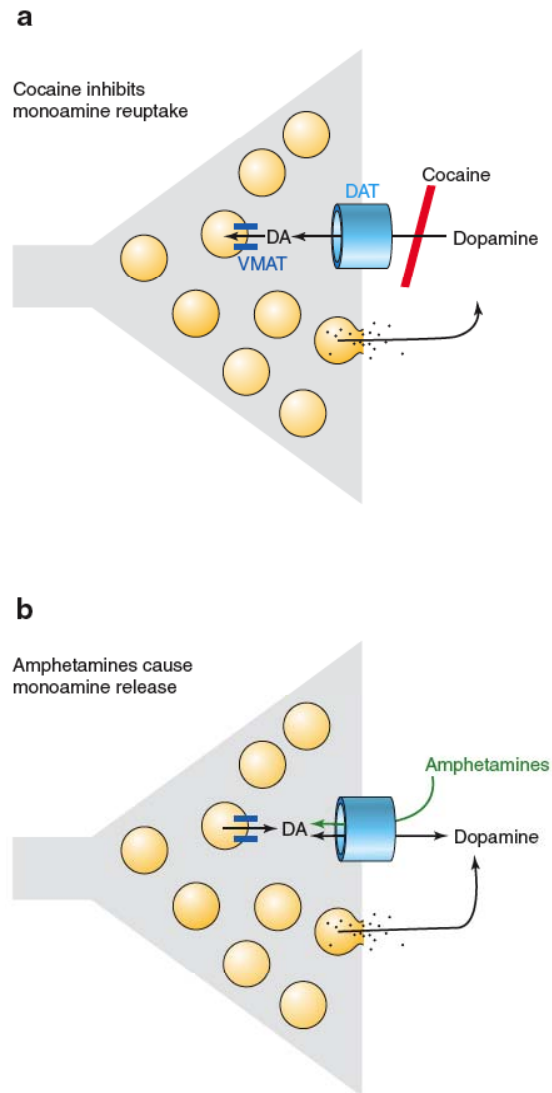
The signal, which originates in the cell body of neurons of the midbrain ventral tegmental area causes the release of dopamine into synapses in various sites in the limbic system, that include the NAcc, amygdala, ventral pallidum and the hippocampus (the mesolimbic pathway). It also releases dopamine into cortical regions, such as the prefrontal cortex, orbitofrontal cortex (OFC) and the anterior cingulate gyrus (aCG), referred to as the *mesocortical pathway* (Wise and Bozarth, 1987; Koob and Bloom, 1988; Di Chiara, 1998) (see Figure 2.). The increases in DA in each of these regions occur in parallel and appear to mediate different aspects of addiction. For example, limbic regions such as the amygdala and hippocampus are involved in conditioned learning in addiction, whereas the prefrontal cortex (PFC),

<sup>5</sup> Nicotine is an atypical addictive drug because it does not increase dopamine as much as psychostimulants and opiates. The addictive property of cigarettes may also depend in part on other chemicals contained in tobacco, such as the monoamine oxidase inhibitors (MAOIs). See Villegier et al. (2006).

OFC and aCG appear to mediate emotional responses to drugs and executive control (that is, higher order decision-making and impulse inhibition). We will discuss these higher cognitive capacities in more detail later (see pp. 65-72).

The sharp increases in extracellular dopaminergic activity that drugs produce in the NAcc, and the ventral pallidum, appear to be central to their capacity to produce addiction. Early research suggested that the increase in DA was particularly important for the acute reinforcing effects of drugs that support continued drug self-administration and the initiation of the cycle of addiction (Koob and Bloom, 1988). Lesions to the NAcc, VTA and ventral pallidum, for example, greatly reduce the self-administration of heroin and cocaine in animals (Roberts et al., 1980; Roberts and Koob, 1982; Hubner and Koob, 1990). Further evidence of the role of increased DA activity in the mesolimbic reward pathway comes from intracranial self-administration studies. Animals will self administer opioids, ethanol, and amphetamines by microinjection directly into mesolimbic structures, such as the NAcc and VTA, but not elsewhere in the brain (Feltenstein and See, 2008). Drugs that reduce DA activity in the brain generally, or locally in the mesolimbic pathway (e.g. drugs that inhibit DA synthesis or DA antagonists that block DA receptors), reduce the self-administration of cocaine, amphetamines, opiates and ethanol (Feltenstein and See, 2008).

The NAcc is a critical part of the neural system that is involved in learning, reward and motivation (Hyman et al., 2006). Everyday rewarding activities, or *natural reinforcers*, such as food, relationships and sex, also produce increases in dopamine in the NAcc, but to a much smaller extent than drugs of addiction (Kelley and Berridge, 2002). Some addictive drugs produce over 10 times more dopamine in the NAcc than natural reinforcers, and their effects last much longer. It is the excess release of dopamine by addictive drugs that is thought to give drugs their rewarding and euphoric effects and hence make drug use so much more appealing than everyday rewarding activities (Wise and Rompre, 1989). See Figure 5.



**FIGURE 3. PSYCHOSTIMULANT INCREASE OF DOPAMINE ACTIVITY AT THE ACCUMBENS**

Stimulants such as cocaine and amphetamine increase synaptic dopamine at the nucleus accumbens by: (a) blocking the dopamine transporter (DAT) (cocaine) which reuptakes dopamine from the synapse, thus increasing the amount of dopamine active in the synapse thereby increasing dopamine signalling; or (b) entering the dopamine neurons via DAT (amphetamine) and causing an increase in dopamine released by the neuron (Source: Hyman et al., 2006).

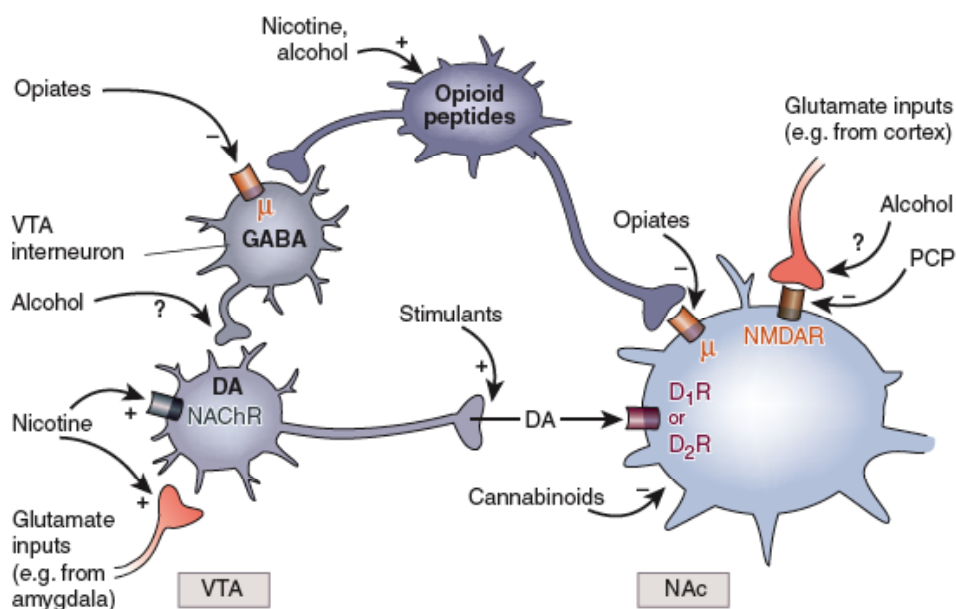


FIGURE 4. ACTIONS OF A VARIETY OF DRUGS ON ACCUMBAL DOPAMINE ACTIVITY

Nearly all drugs of addiction act by increasing the release of dopamine in the nucleus accumbens (NAcc; bottom right). This increase may be direct, such as the case with stimulants, which increases the release of dopamine by neurons of the ventral tegmental area (VTA; bottom left). Other drugs of addiction (e.g. alcohol, opioids, cannabis and nicotine, increase dopamine activity indirectly, by influencing neurons which then change the amount of dopamine released into the NAcc. This may be the result of an inhibition of a disinhibiting response, such as occurs with the opiates, as well as an excitatory response (e.g. nicotine). Note: '+' refers to an excitatory response, '-' denotes inhibition (Source: Hyman et al., 2006).

Imaging of human brain function during intoxication shows that increases in accumbal dopamine are correlated with subjective reports of euphoria (Volkow et al., 2004a). This is clearest for stimulant drugs: for these drugs the greater the dopamine release in the NAcc, the greater the euphoria that is reported (Laruelle et al., 1995; Drevets et al., 2001). This is not always the case, however. There are many studies which show a poor correlation between subjective states of pleasure and drug-taking (Robinson and Berridge, 2000). As addiction progresses, the consumption of larger amounts of drugs does not increase the pleasure experienced; in fact in most cases, rewarding or euphoric experiences decrease with increasing drug use. Moreover, nicotine, a highly addictive drug, increases dopamine release in the NAcc at

considerably lower levels than other drugs and without producing any significant euphoric effects (Nisell et al., 1994; Balfour, 2004; Koob and Le Moal, 2006).

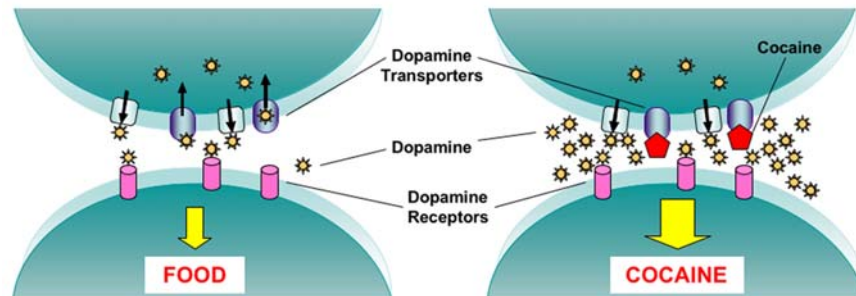


FIGURE 5. REWARDING ACTIVITIES INCREASE DOPAMINE SIGNALLING

Drugs of addiction act on the brain's reward pathway to cause enormous increases in dopamine activity in the nucleus accumbens. Everyday activities also increase dopamine activity in this reward pathway, but to a much smaller extent. The exaggerated release of dopamine due to drugs such as cocaine produces changes in other parts of the nervous system that focuses attention on drug use (Source: Adapted from NIDA website).

Recent research has suggested that dopaminergic release within the NAcc may be more related to the *saliency*, that is, to the significance of stimuli associated with drugs, or the *learning of reward*, rather than their rewarding or euphoria-inducing effects. While there is uncertainty about whether all drugs produce a measurable release of DA in the NAcc (Nutt and Lingford-Hughes, 2008), cues associated with drug use do increase DA levels (Volkow et al., 2006; Wong et al., 2006). In addition, researchers have found increased DA release immediately prior to the initiation of self-administration (Melendez et al., 2002; van Erp and Miczek, 2007). It has therefore been suggested that increases in accumbal DA in response to addictive drugs may reflect the "anticipation" of drug consumption.

In a series of key experiments, Schultz and colleagues showed that while initially VTA DA neurons fire when drugs are used, increased DA activity is transferred to the events or stimuli associated with the use of the drug (Schultz et al., 1997; Schultz, 2007). These drug-paired, or conditioned cues, are able to increase DA firing. Schultz showed that there is however, a decrease in DA firing if an expected

reward does not follow the presentation of conditioned drug cues. This research supports the hypothesis that once someone is addicted, DA comes to play a more important role in signalling the significance of a cue than in mediating the effects of the drug itself. This response to cues associated with reward suggests that sensitisation of accumbal DA release may enhance the motivational salience of drug-associated stimuli (Schultz et al., 1997).

Robinson and Berridge argue that, by associating large increases in dopamine with drug taking and drug stimuli, learning drives the motivation to take drugs independently of any pleasure that their use may bring. As repeated drug use gains enhanced salience over normal or everyday reinforcing activities, a conditioned association between the drug's effects and associated external cues is strengthened. Rats treated with dopamine antagonists fail to associate the effects of drug use with the context in which the drugs were given (Hyman, 2005). Thus events may be perceived as salient not because of their rewarding effects, but because they are seen as novel or grab attention. Therefore, it is suggested that these systems do not mediate the pleasurable or euphoric aspect of drug-taking so much as a "subcomponent of reward" that we call *salience* (Robinson and Berridge, 2000, p. s94).

This research suggests that dopamine functions as a signal for learning about experiences, rather than simply producing pleasure. It is released when a rewarding experience is new, better than expected, or unanticipated (Schultz et al., 1997; Schultz, 2006). It plays an important role in identifying and remembering which activities or experiences are worth pursuing and repeating. Drugs of addiction act upon this natural reward pathway to motivate its repeated use. This property of dopamine may explain why aversive or unpleasant stimuli are also able to motivate behaviour (Robinson and Berridge, 2000), and why drug use persists long after its immediate effects cease to be rewarding (Robbins et al., 2007).

It has also been hypothesised that the difference between addictive drugs and "natural" rewards is the ability of drugs to bypass an homeostatic feedback mechanism (Robinson and Berridge, 2000). For example, when we are hungry, stimuli that predict food availability (e.g. the smell of chips), readily grasp our attention. However, if we have just eaten, the same smell may be very strong and we will hardly notice it, or even find it aversive. Because addictive drugs bypass this feedback, stimuli that predict drug availability are always able to grab the attention of

addicted persons and provoke in them an intense desire to use the drug (i.e. craving).

We will return to the role of memory and learning, in particular the neurobiology of associative learning, in addiction below. While changes in dopamine activity are important in the development and “learning” (acquiring) of an addiction, they cannot explain all aspects of addiction, such as the ability of drug-related events to elicit craving long after abstinence has been achieved, an effect that can lead to a return to drug use. Before shifting to the important issue of craving and relapse, we will first discuss the significant role that withdrawal symptoms play in preventing the cessation of drug use, and the role that other key neurotransmitter systems may play in producing the rewarding effects of addictive drugs.

### **Dopamine, Withdrawal and Negative Reinforcement**

The acute, reinforcing effects of addictive drugs occur against a background of a normal functioning dopaminergic reward system. Volkow and others (e.g. Volkow et al. (2009) and Cosgrove (2010)) have argued that while drug use initially increases dopamine release, chronic use of some drugs (e.g. cocaine, methamphetamine, nicotine and cannabis) dramatically decreases DA activity (Volkow and Fowler, 2000; Heinz et al. 2005; Fehr et al. 2008; Sevy et al. 2008). They argue that repetitive release of dopamine leads to a *down-regulation* of dopamine signalling and a dampening of activity in the reward pathway (Volkow et al. 2009). The neurochemistry of the reward pathway appears to adapt to the repeated abnormal elevations in dopamine release by producing a compensatory reduction in dopamine activity. This seems to occur largely as the result of a decrease in the number of post-synaptic dopamine receptors in brain regions such as the striatum (Volkow et al. 2009).

Dopamine down-regulation significantly reduces activity in the dopaminergic reward system and thereby appears to reset the threshold for activating the reward system. The NAcc accordingly becomes less sensitive to the rewarding effects of everyday activities in chronic drug users. Koob refers to this adaptation in the reward pathway as **allostasis**: a dysregulation of normal homeostatic functioning (Koob and Le Moal, 2001). The dampening of dopaminergic activity in the reward pathway also leads to an aversive state upon abrupt cessation of drug use, that is, **withdrawal**. Abrupt cessation of chronic drug use leads to a decrease in dopamine release (Weiss et al., 1992; Chefer and Shippenberg, 2002) and to elevated thresholds of reward that may

prompt drug-seeking in order to relieve the aversive symptoms of withdrawal. Natural reinforcers are unable to reach this threshold but drugs of abuse are still able to activate the reward centres. In this way, relief of withdrawal symptoms can become a negative reinforcer that like thirst or hunger (Hutcheson et al., 2001), motivates continued drug-seeking (Koob and Le Moal, 1997) and presents a significant impediment to enduring abstinence. A summary of the major neurobiological theories of addiction is provided in Table 2 on pages 33-35.

The majority of neuroscience research on addiction (estimated to be 85%) is funded by the National Institute on Drug Abuse (NIDA). NIDA's leaders (e.g. Leshner and Volkow) have promoted one view of this work: the view of addiction as a "chronic relapsing brain disease". Many neuroscience researchers have argued for a broader view and caution against prematurely accepting the, albeit highly plausible, dopamine hypothesis until these studies have been replicated in larger and more diverse populations addicted to a broader range of drugs. As discussed below, there is also evidence that other neurotransmitter systems are involved in addiction .

### **Dopamine-independent Reinforcement of Addictive Drugs**

There is also animal research that complicates the standard account of the role of DA in the acute rewarding or pleasurable (that is, liking) effects of addictive drugs. This includes evidence that opioids, alcohol, amphetamines and nicotine can produce their reinforcing effects through mechanisms that are independent of DA (van Ree et al., 1999). NAcc-specific lesions of dopaminergic neurons or DA receptor antagonists, for example, while blocking psychostimulant self-administration, fail to completely attenuate the self-administration of opioids or alcohol (Feltenstein and See, 2008). The administration of the dopamine-antagonist, pimozone, does not block euphoria due to amphetamine consumption in amphetamine-naïve individuals (Brauer and De Wit, 1997). Similarly, the administration of dopamine antagonists, (either systemically or directly into the NAcc) does not alter the responses maintained by intravenous heroin self-administration. Further, selective destruction of presynaptic dopaminergic nerve terminals in the NAcc, using the catecholamine selective neurotoxin 6-OHDA (6-Hydroxydopamine), does not attenuate intravenous opiate self-administration (Pettit et al., 1984; Dworkin et al., 1988).

These observations are supported by evidence that drugs which block the neurotransmitter systems on which some addictive drugs act can block the effects of other addictive drugs. For example, the opioid receptor antagonist, *naltrexone*, also



reduces alcohol consumption, the cannabinoid receptor antagonist, *rimonabant*, is used to treat obesity, and the acetylcholine partial agonist, *varenicline*, appears to be useful in treating alcohol dependence (Nutt and Lingford-Hughes, 2008) as well as nicotine dependence. In addition, some researchers have been unable to repeat earlier experiments that found an increase in accumbal DA, for example, in response to acute psychostimulant (Volkow et al., 1997) or opioid (Daglish et al., 2008) administration. Future research will hopefully resolve these discrepancies.

Recently, research has begun to focus on the involvement of a number of other neurochemicals and neurotransmitter systems in the reinforcing effects of addictive drugs. These include: the opioids, glutamate and gamma-aminobutyric acid (GABA), noradrenaline, serotonin and cannabinoids (Goodman, 2008), some of which are discussed below.

### *Opioids*

The brain's endogenous opioid system comprises a number of different neuropeptides (the endorphins, enkephalins and dynorphin) that interact with one or more of the three opioid receptor types – mu, delta and kappa – found in the brain. Mu receptors mediate the pleasurable effects of opiate drugs, such as heroin and morphine, and endogenous (naturally occurring) opioids, such as the endorphins. Mice that do not possess mu receptors will not self-administer opioids (Becker et al., 2000). The identification of the mu receptor as the site of action for heroin and other opioids led to the development of opioid antagonists, such as naloxone and naltrexone that prevent the rewarding effects of heroin by binding to the same receptors. These antagonists are also clinically useful in alcohol addiction, probably because alcohol also releases endorphins in the brain.

Changes in brain opioid receptors may also play a part in addiction to other drugs. Brain imaging studies have shown that opioid receptors are increased in persons who are withdrawing from cocaine (Zubieta et al., 1996), opioids (Williams et al., 2007) and alcohol (Heinz et al., 2005). Opioid antagonists also reduce the threshold for self-stimulation in ICSS paradigms (a measure of the reinforcing capacity of addictive drugs)<sup>6</sup> as do DA receptor blockers (Schaefer, 1988). This may explain why opioid antagonists, such as naltrexone, appear to be useful in the treatment of addictions to alcohol and food. Both intracranial and systemic administration of opioid

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<sup>6</sup> Drugs that activate the dopaminergic system and increase DA levels in the NAcc also facilitate brain stimulation reward (increase thresholds for self-stimulation).

receptor antagonists not only attenuate opioid self-administration as expected, but also administration of ethanol (Feltenstein and See, 2008).

### *Cannabinoids*

Endocannabinoids are a family of widely expressed neurotransmitters. Scientists have identified endogenous cannabinoids (e.g. anandamide) that activate the two cannabinoid receptors (CB1 or CB2). The active ingredients in cannabis, delta-9-tetrahydrocannabinol (THC) and cannabidiol, also act on these receptors. Cannabinoids increase the reinforcing effect of a number of drugs of addiction by post-synaptically increasing dopaminergic activity (e.g. ethanol, opioids, cocaine) (Caille and Parsons, 2003; Colombo et al., 2005). The use of CB1 receptor antagonists reduces the self-administration of both ethanol and opioids in animals, suggesting that the endogenous cannabinoid system is also involved in the reinforcing effects of drugs in addition to cannabis, and in the development of addiction (Caille and Parsons, 2003; Colombo et al., 2005).

### *Glutamate*

Glutamate is the primary excitatory neurotransmitter and is ubiquitously expressed in brain. Glutamate also mediates synaptic plasticity; the long-term changes at synapses that influence the strength of connectivity between neurons and produce learning and memory. Synaptic plasticity is an important aspect of the “learning” of addictive behaviours (see below for a more detailed discussion, pp. 60-65). The cortico-striatal glutamate pathway has been shown to be important in both the initiation and expression of many of the addiction-related behaviours, including drug-seeking, conditioned place preference, and locomotor sensitisation (Kalivas et al., 2008). Changes in glutamate activity are also involved in many of the deficits in higher cognitive functions associated with addiction. A detailed discussion of the role of glutamatergic activity is beyond the scope of this report. Interested readers are directed to a recent review (Kalivas et al., 2008).

Glutamate has been the subject of significant research in the past 15 years as a potential target for pharmacological treatment of addiction. The wide expression of this signalling molecule in brain, however, has meant that treatments often have significant side-effects. The development of pharmacological agents that target specific receptor subtypes has opened up the possibility of more effective glutamatergic treatments of addiction which we discuss later in the chapter on treatments of addiction.

### *Implications for Research*

Some argue that the focus on the role of DA in addiction has inhibited the development of more effective pharmacological treatments targeting these other neurotransmitter systems. Research is now beginning to uncover changes in these systems, differences between the various drugs of addiction in these effects, and individual differences between people with different addictions that may be clinically useful. Such research has the potential to provide more effective, personalised pharmacological treatments of addiction.

Although the GABA, glutamate, opioid and endocannabinoid systems are significantly involved in the *acute* reinforcing effects of addictive drugs (particularly drugs other than psychostimulants), the prevailing view is that the dopaminergic reward pathway is central to the reinforcing properties of drugs, and the initiation of the cycle of addiction. While changes in these additional neurotransmitter systems are indeed important in addiction, most exert their major influence through the dopaminergic reward system (Goodman, 2008). The dopaminergic reward pathway appears to be under the regulatory control of these other neurotransmitter systems.

There are potentially dozens of neurotransmitters and other signalling molecules that are involved in addiction to some degree. Each of these systems has between 2 and 15 receptor targets. A complete discussion of all the neurochemicals involved in addiction is beyond the scope of this report. We can only refer interested readers to a recent review in *Biochemical Pharmacology* (Goodman, 2008). Those interested in the roles of noradrenaline and serotonin can consult the comprehensive review in the same issue by Tassin (2008).

### **Limitations of Hedonic Theories of Addiction**

The dopamine theory of addiction is often referred to as an *hedonic model* of addiction. This is because it assumes that individuals use addictive drugs in order to experience their pleasurable effects and to avoid withdrawal symptoms. While reward and withdrawal partially explains the desire of addicted individuals to take drugs, the initiation of drug use and the difficulty in achieving abstinence, it does not explain the reported “compulsion” or “loss of control” over drug use that human addicts report (O'Brien et al., 1998; Tiffany, 1998). While research has shown that changes in dopamine, opioids, glutamate and other neurotransmitters in response to drug use are necessary for developing addiction, large increases in dopamine activity in the limbic regions are not sufficient for the development of addiction as they occur in both

addicted and non-addicted individuals. Dopamine release may explain why drugs of addiction are rewarding or reinforcing, but it does not explain why some users stop using rewarding drugs while others continue to use these drugs after their rewarding effects have ceased and in the face of negative social and physical consequences of use.

More significantly, the hedonic model does not explain why individuals can relapse to drug use after months and even years of abstinence, long after the symptoms of withdrawal have abated. In seeking to explain these phenomena recent neurobiological research has focused more on persistent neuroadaptations in the brain that can elicit craving and lead to relapse, months after abstinence has been achieved. This includes research on the effects of chronic drug use on: memory and learning (e.g. associative learning); responses to stress; craving; and behavioural control. Recent research has begun to explain the persistent nature of addictive behaviour in terms of a series of neuroadaptations in human cognitive systems.

As we have shown, there still exists uncertainty about the precise role that DA plays in addiction. Specifically, there is significant unresolved debate among addiction neurobiologists about whether dopamine is involved in: reward, incentive salience or motivation, or learning. Despite disagreement about its specific role, it is likely that drug-induced changes in dopamine activity are central to the development of addictive behaviours. This review will not attempt to resolve these debates, but will rather focus on areas where there is general consensus. For a thorough discussion see the 2007 review and commentary in *Psychopharmacology* (Berridge, 2007; Robbins and Everitt, 2007), or Kelley and Berridge (2002).

To summarise, current research suggests that DA is less involved in the unconditioned rewarding effects of drugs of addiction than was first thought. It appears to have more to do with the persistence of addictive behaviours, such as enhancing the motivating quality (i.e. incentive salience) of stimuli or events that are associated with the consumption of drugs (e.g. conditioned learning). These adaptations appear to be responsible for the initiation of intense drug cravings, months after abstinence is achieved, and may play a role in return to drug use. In the next section, we review evidence from animal studies that investigate the neuroadaptations in the dopaminergic and other neurotransmitter systems that can lead to relapse and the maintenance of addiction.

## ***Animal Models of Drug Relapse and Reinstatement***

The ability for events to induce craving after months of abstinence and trigger a return to drug use is a central feature of addiction. It is what makes addiction so difficult to overcome in the long-term. Research suggests long-lasting neuroadaptations in the central circuits of the brain may be responsible for the induction of craving and the triggering of relapse.

There are several factors that can be potent triggers of relapse: exposure to events or stimuli associated with drug use (conditioned drug cues); stress or negative mood states; and exposure to small amounts of the drug of addiction, called *drug priming*. Animal studies have identified a number of long-lasting neuroadaptations in brain pathways involved in addiction that may explain these observations. These include learning and memory, stress and affective regulation.

The study of relapse to drug use in animals most often employs extinction-reinstatement models of addiction. For example, animals are trained to self-administer a drug of addiction by pressing a lever for an extended period of time. This behaviour (pressing the lever) is then extinguished by stopping drug administration. This model allows investigators to measure the ability of stimuli such as stress (e.g. foot shock) or cues previously associated with drug use (e.g. lights or odours), to reinstate drug self-administration via lever pressing (Shaham et al., 2003). This approach can also be used to study other behaviours, such as conditioned place preference. Conditioned drug cues, stress and drug priming all reinstate drug-seeking behaviours (e.g. lever pressing). These phenomena are similar to the behaviour of addicted humans, in whom events associated with drug use, such as the pub or drug associates, can produce a relapse to drug use months after abstinence has been achieved.

Reinstatement has enabled scientists to probe the neurocircuitry of relapse-like behaviour in animals (Shaham et al., 2003), that is taken by many to provide a model of drug craving in human addicts (Koob, 2000). Some researches have cautioned against generalising results from the model to clinical addiction (Katz and Higgins, 2003). Reinstatement models resemble human addiction (and so have face validity) and they are good predictors of human behaviour in response to events or drugs (and so have predictive validity). It is less clear, however, that the animal models and human phenomena involve the same neurochemical processes (and so possess

construct validity) (Katz and Higgins, 2003; Epstein et al., 2006). Therefore, we will limit out interpretation of reinstatement studies in animals to relapse, or more correctly relapse-like behaviour rather than craving.<sup>7</sup>

It has generally been assumed that craving is something that is greatest immediately after abstinence has been achieved, and then decays with time. However, recent research suggests that the opposite may in fact be the case (Grimm et al., 2001; Lu et al., 2004). These researchers found in rats, that craving in fact progressively worsened over a two month period. This phenomena that was referred to as the ***incubation of craving*** may have significant implications for the treatment of human addiction. More studies in human subjects are needed to see if this also holds in addicted humans. A full discussion of the incubation of craving is beyond the scope of this report. Interested readers are directed to Bossert et al. (2005).

### **Associative Learning or Conditioned Incentive Learning**

Key areas of the brain that are involved in learning also play a key role in addiction (Everitt and Robbins, 2005). Addiction involves learning new habits (e.g. drug use) so it is not surprising that changes in the neural pathways that underpin learning and associative memory (e.g. conditioned responses) are also involved in the development of addiction. A neural system involved in learning and memory is the mesolimbic pathway, including the NAcc, amygdala, hippocampus, and the striatum (caudate and putamen). These neural systems are implicated in: conditioned incentive or associative learning (NAcc and amygdala); habit learning (the caudate and putamen); and declarative memory (the hippocampus). The prefrontal cortical regions also appear to play an important role in associative learning. In this review, we focus particularly on associative learning because this is the most clinically relevant form of memory and learning in addiction, and appears to be particularly important in explaining craving, relapse and the persistence of addiction.

As noted above, drug-related cues can elicit craving in abstinent drug users and trigger relapse (O'Brien et al., 1998). Animal studies of Pavlovian conditioning consistently show that a single exposure to a conditioned stimulus is enough to reinstate addictive behaviours in animals that have been abstinent for long periods of time (Gold and Koob, 1989). In particular, the hippocampus and the amygdala, have been shown to be critical in the acquisition, consolidation and expression of drug-

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<sup>7</sup> It is beyond the scope of this report to review the arguments about the validity of animal models of relapse and craving. We refer interested readers to Geyer and Markou (1995) and Epstein et al. (2006).

stimulus learning that appears to drive relapse to drug use (Weiss et al., 2000; See, 2005). This research suggests that changes in brain functioning that leads to the formation of habits gives special salience to cues related to the contexts in which drugs are used. These learned drug associations can be cues for internal states of craving that lead to relapse.<sup>8</sup>

Cue-induced reinstatement of drug use has been shown to involve the dorsomedial prefrontal cortex (dmPFC) and the basolateral amygdala (BLA) connections with the NAcc (McLaughlin and See, 2003). Dopamine and glutamate are the central neurotransmitters involved in this process. Cue-induced reinstatement of drug-seeking has been shown to activate the dmPFC, by the induction of early gene expression (e.g. Fos).<sup>9</sup> This can be blocked by D1 receptor antagonists (Ciccocioppo et al., 2001; Koya et al., 2006), suggesting that DA has a role in this process. Cue-induced reinstatement is also inhibited by pharmacological deactivation of the dmPFC. Similar research has implicated the lateral OFC (Fuchs et al., 2004).

Disruption of the basolateral amygdala suggests that it too is required for the formation of stimulus-drug associations and the expression of conditioned cue-induced drug-seeking during relapse (Weiss et al., 2000). The expression of cue-induced reinstatement in the BLA also appears to be mediated by DA: drug-related cues produce significant release of DA, and DA receptor antagonists attenuate the acquisition (Berglund et al., 2006) and expression (See et al., 2001) of conditioned-cue reinstatement.

The NAcc also appears to be involved in the cue-induced reinstatement of drug use. Exposure to drug-associated cues activates the NAcc and the inactivation of the NAcc core reduces the capacity of cues to induce reinstatement (Fuchs et al., 2004; Dayas et al., 2007; Di Ciano et al., 2008). Again, this effect appears to be mediated by DA (Weiss et al., 2000). The neurotransmitters glutamate and acetylcholine also appear to be involved in accumbal cue-induced reinstatement of drug use (Cornish et al., 1999; Zhou et al., 2007).

Collectively, these results suggest that reinstatement of drug-seeking behaviour, and therefore possibly relapse to addiction, involves dopaminergic and glutamatergic

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<sup>8</sup> More on details of the different processes operating in each of these neural regions can be found in White (1996), Robbins and Everitt (2002), Wise (2004) and Everitt and Robbins (2005).

<sup>9</sup> Fos is an early gene that is expressed when a neuron has been recently stimulated, and is therefore seen as a marker of neuronal activation

interactions in the NAcc core and the dmPFC and BLA. Cue induced reinstatement, however, is not controlled by DA alone. It also requires several additional neurotransmitters or neurochemical systems. Next we look at one such neurochemical system that has received significant research attention in the last few years.

#### *Orexins and the Neuropeptide System*

Recent research has suggested that a number of neuropeptides may play an important role in the formation and expression of addictive-like behaviours, such as drug-seeking and relapse. The neuropeptides include signalling molecules such as the endogenous opioids, Substance P, and neuropeptide Y (NPY). There has been considerable interest in this system as a novel therapeutic target for treating addiction to drugs and eating disorders. It is beyond the scope of this report to discuss all neuropeptides that play a role in addiction. Interested readers should refer to reviews by Cowen et al. (2004) and Boutrel (2008). We briefly discuss the role of stress neuropeptides (e.g. CRF) on pp. 58-9 and the endogenous opioid peptides on p. 48-9.

Of particular interest in recent years is the family of neuropeptides called the *hypocretins*, or *orexins*. Orexins play an important role in the regulation of everyday behaviours such as child birth, feeding, arousal and sleep. Research suggests that the lateral hypothalamic orexin system is also important in conditioned drug-seeking and relapse (Harris et al., 2005). Orexins are secreted by hypothalamic neurons into the VTA where they can influence DA signalling. Two orexin peptides – orexin A and B – and the two orexin receptors – orexin 1 and 2 – have been identified (Sakurai et al., 1998). Harris (2005) showed that orexins are required for the development of conditioned drug-seeking behaviour. Orexin signalling in the VTA is necessary for the development of addictive-like behaviours, since blocking the orexin 1 receptor prevents the development of locomotor sensitisation, an animal model used to measure addictive behaviours, such as the reinstatement of drug-seeking.

This effect appears to be mediated by the induction of neuroplastic changes in the VTA (Borgland et al., 2006). Orexin A is required for the induction of synaptic changes necessary for the development of drug-seeking behaviours (see Figure 6.). This change appears to be mediated by promoting the insertion of N—methyl D-aspartate receptors (NMDA<sub>R</sub>) receptors into the excitatory postsynaptic membrane of DA cells in the VTA, via a PKC dependent pathway (Borgland et al., 2006). The



insertion of NMDA receptors provides an initial increase in excitatory signalling on the postsynaptic DA cells of the VTA. This can lead to more long term plastic changes at the excitatory synapse by the induction of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) mediated signalling. These neuroplastic changes provide the learning necessary for cues associated with drug use to trigger a reinstatement of drug-seeking behaviours (Carr and Kalivas, 2006). Importantly, this induction of AMPA mediated learning was blocked by pre-exposure of an orexin A antagonist prior to drug administration (Borgland et al., 2006).

The orexin system has also been shown to regulate the cue-induced initiation of drug-seeking behaviours in alcohol-dependence (Lawrence et al., 2006). The conditioned (cue-induced) reinstatement of alcohol-seeking behaviour was completely blocked by an orexin 1 receptor antagonist (SB-334867) in alcohol-preferring rats. The orexin antagonist also attenuated operant responding (lever pressing). Cues previously associated with alcohol exposure activate orexin-secreting neurons (located in the lateral hypothalamus) that drive the reinstatement of alcohol-seeking behaviours (Dayas et al., 2008; Hamlin et al., 2008). Thus, orexins appear to be involved in the cue-induced relapse, at least in alcohol, but not in the development of alcohol-liking.

These studies have provided convincing evidence that orexin-containing hypothalamic neurons are necessary for repeated exposure to drugs of abuse to induce neuroplastic changes at glutamatergic synapses on DA neurons of the VTA that can lead to a relapse to drug use once abstinence has been achieved. More research is required to understand precisely what the orexin signal is conveying (e.g. reward: desire vs. satiety). A recent study by Boutrel suggests that the induction of these synaptic changes may occur in the presence of any motivating signal irrespective of whether it has positive or negative valence (Boutrel et al., 2005).<sup>10</sup>

Recent research has implicated other hypothalamic neuropeptides in drug reward and seeking, such as the CART (cocaine and amphetamine regulated transcript) neuropeptide (Dayas et al. 2008). As with the orexin neurons, reinstatement of drug-seeking behaviour in response to conditioned cues associated with alcohol appears to activate hypothalamic CART neurons (Dayas et al., 2008). Hypothalamic neuropeptide neurons, such as the orexins and CART, are responsive to cues

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<sup>10</sup> Boutrel showed that the induction of these plastic changes can also be prevented by blocking the brain's stress pathway (Boutrel, 2008).

signalling food reward (Kelley, 2005; Mieda, 2004). Thus, research into the hypothalamic neuropeptide system may also provide further insights into “behavioural addictions”, such as compulsive eating (Kelley, 2005).

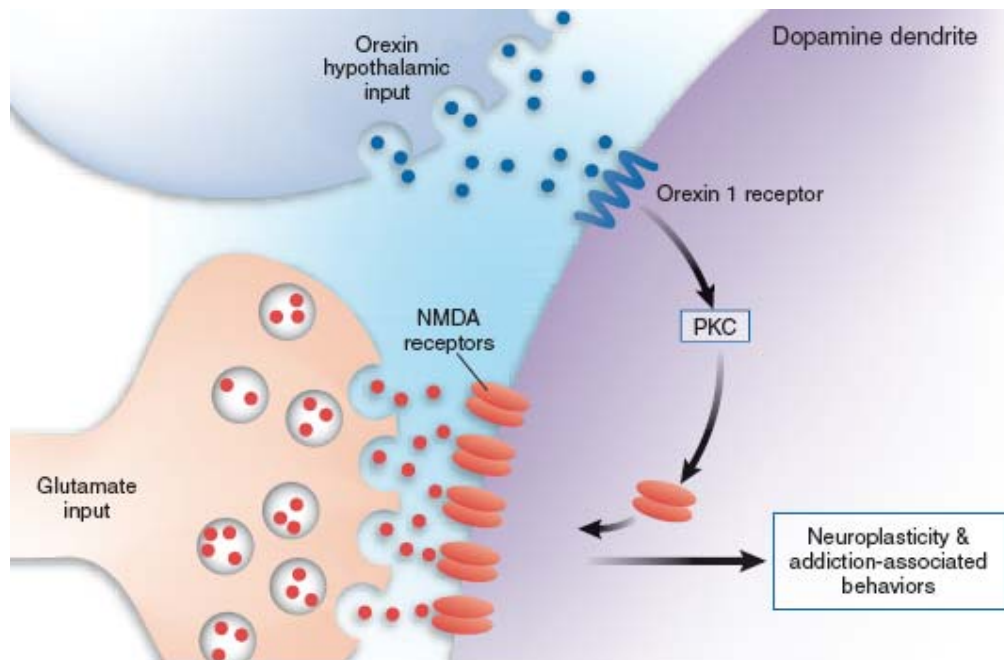


FIGURE 6. OREXINS ROLE IN ASSOCIATIVE LEARNING IN ADDICTION

Orexins released by the hypothalamic orexinergic neurons into the VTA can lead to the acquisition of drug-cue associations by inducing the insertion of NMDA receptors into the excitatory post synaptic membrane of dopaminergic neurons on the VTA. This occurs via a PKC-dependent mechanism, and is essential for the ability of drug-cues to induce addictive behaviours in animals that are believed to model relapse to drug use. (Source: Carr and Kalivas (2006)).

### **Stress, Affect Regulation and Relapse**

Stress is a significant contributor to relapse to addictive drug abuse following abstinence (Koob and Le Moal, 2001; Koob and Kreek, 2007; Koob, 2008). Observational studies of human addicts report that stress is a particularly potent trigger for relapse (Koob, 1999a). Stressful events, particularly when they occur repeatedly, increase negative affect and can also induce strong drug cravings that often lead to relapse (Sinha et al., 1999).

The chronic use of addictive drugs can dysregulate the brain's stress system. It produces alterations in corticosterone (in rats), cortisol releasing factor (CRF) and adrenocorticotrophic hormone (see Kreek and Koob (1998), Koob and Kreek (2007) and Koob (2008) for reviews). Koob and colleagues (1997, 2008) have suggested that these adaptations in the stress system, hormone/neurotransmitter release and receptor expression, may be the result of an attempt by the brain to maintain homeostasis in the face of chronic drug abuse. Consequently, after abrupt cessation of drug use, these neuroadaptations act unopposed to produce many of the negative emotional states that are characteristic of drug withdrawal and enhance the ability of stressful stimuli to produce relapse.

Chronic drug use produces neuroadaptive changes in an "anti-reward" pathway that includes the hypothalamic-pituitary-adrenal (HPA) axis and the neuropeptide, corticotropin releasing factor (CRF) (Koob and Le Moal, 1997; Koob and Le Moal, 2008). Individuals in acute drug withdrawal show increased activity of CRF in the HPA and regions of the limbic system, and increased release of noradrenaline and dynorphin. All of these effects predict relapse to drug use. CRF receptor antagonists have been shown to reduce drug self-administration in animals (Koob and Le Moal, 1997; Koob and Le Moal, 2008). They are currently being investigated as potential treatments for addiction in individuals who are especially susceptible to relapsing in the face of stress.

Stress and stress hormones can also directly affect the reward pathway to make individuals more vulnerable to developing drug addiction. While both acute and chronic stress affect the dopaminergic reward pathway, they have different effects on drug use.

Acute stress triggers the release of dopamine in the neural reward pathway that can motivate drug seeking in dependent individuals which may lead to relapse (Marinelli and Piazza, 2002). Studies of animal models of addiction show that stress (e.g. footshock) or the neurochemical induction of stress-like symptoms (e.g. by giving a noradrenaline alpha-2 receptor antagonist, yohimbine) can lead to the resumption of drug-seeking in abstinent, drug dependent rats (McFarland et al., 2004; Feltenstein and See, 2006). Inactivation of the NAcc, dmPFC and VTA attenuate stress induced reinstatement of drug seeking. However, research suggests that the central nucleus of the amygdala (CeA) and the lateral bed nucleus of the stria terminalis (BNST) play

an important role in the ability of stress to reinstate addictive behaviour. CRF and noradrenaline are the primary neurotransmitters that are involved in stress-induced reinstatement in these regions: CRF administration in the CeA or BNST and pharmacological reduction of noradrenaline activity both attenuate the reinstatement of drug seeking by footshock (Shaham et al., 1997; Erb and Stewart, 1999; Erb et al., 2000).

Chronic stress releases hormones that trigger the release of dopamine into the NAcc (Stamford et al., 1991). Repeated increases in stress hormones, and consequent dopamine release, sensitise the reward system over a long period of time (Marinelli and Piazza, 2002). Chronic stress therefore results in apparent neuroadaptations within the reward pathway that dampen dopaminergic activity and reduce sensitivity to normal rewards. These neuroadaptations to chronic stress (that are thought to be due to a reduction in the number of dopamine receptors) also lead to *anhedonia* - the inability to experience pleasure. This sensitisation of the reward system by chronic stress, the down-regulation of the dopamine receptors and the development of anhedonia, are also thought to be involved in depression. This may explain why dopamine agonists that ameliorate these effects are also effective in treating depression.<sup>11</sup> This sensitisation of the reward system makes former addicts who experience stress more responsive to drugs of abuse, and therefore, more vulnerable to addiction if they use drugs (Marinelli and Piazza, 2002). The sensitisation can also persist well after the stress has abated. Genetically-based sensitivity to stress or anxiety can make individuals more sensitive to the effects of stress, and hence more vulnerable to developing addiction. This is discussed in greater detail below (see pp 72-77).

## **Molecular Biology in Addiction**

There is increasing evidence that chronic drug use, and the hypothesized changes in dopamine signalling outlined above, produce neuroadaptations at the molecular and cellular level in the neurocircuitry that maintains addiction; that is, the mesolimbic and mesocortical systems. Chronic drug use leads to plastic changes at synapses in key neural circuits that are believed to be responsible for characteristic addictive behaviours, such as craving, relapse and impaired decision-making and control over drug use. See Figure 7.

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<sup>11</sup> For further information see Willner (1997) and Willner et al. (2005).

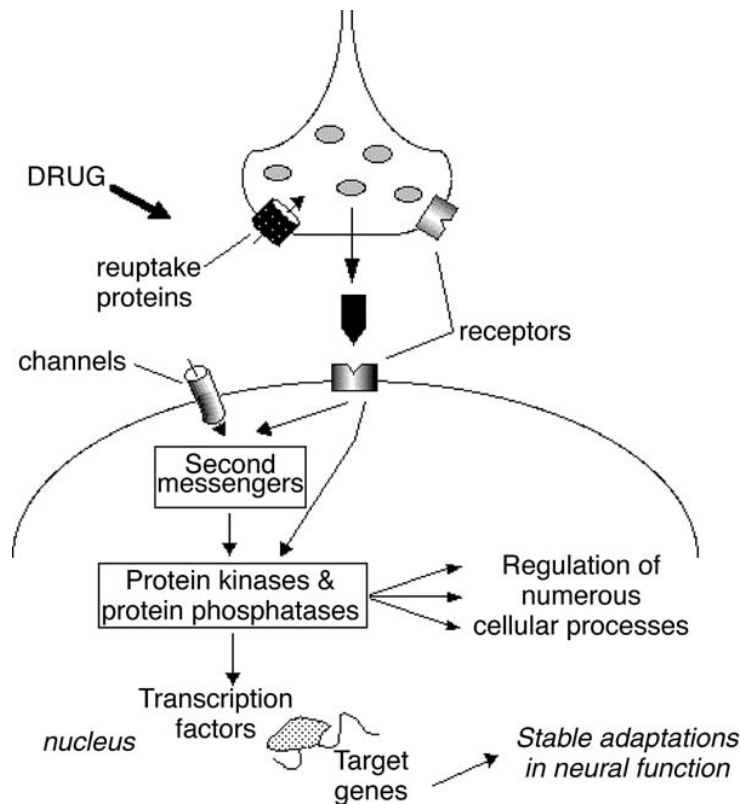


FIGURE 7. SCHEMATIC DIAGRAM OF MOLECULAR CHANGES IN NEURAL CELLS IN RESPONSE TO DRUG USE

Addictive drug use can produce downstream changes in intracellular (or second) messenger pathways that are believed to mediate changes in behaviour. It may also affect the regulation of gene expression, that is, produce *epigenetic* effects. These second messenger pathways also influence other cellular processes, such as cell-to-cell signaling. All these cellular processes are referred to collectively as *synaptic plasticity*. (Source: Nestler (2004)).

### Synaptic Plasticity in Addiction

There has been significant research since the early 1970's to identify the molecular and cellular processes that strengthen or weaken the connectivity between neurons; a process first hypothesised to exist in 1894 by the pioneering neuroscientist, Ramon y Cajal (Kauer and Malenka, 2007). This process which is now called *synaptic plasticity* refers to the molecular and cellular process by which information,

experience or learned responses are represented in the brain by changes in neural connections.

The molecular machinery for synaptic plasticity was first observed in the excitatory glutamate synapses of the hippocampus (Bliss and Lomo, 1973). This molecular process is referred to as *long term potentiation (LTP)*. It describes how observed behaviours or learning are encoded by molecular and cellular changes in neural connectivity. Synaptic plasticity is an activity-dependent process that allows synapses to be strengthened (LTP), or weakened (*long-term depression* or LTD).

The signalling processes involved in synaptic plasticity are extremely complex and can vary between different brain regions. This research is also in its infancy so there is significant uncertainty about the specific details. Consequently only a brief overview of this area of research is provided here, with the focus on those areas in which there is consensus. It is also not possible in this report to review all of the molecular and cellular processes involved in synaptic neuroadaptations. Only N—methyl D-aspartate receptor (NMDA<sub>R</sub>)-dependent LTP is discussed to provide readers with some appreciation of the kinds of molecular and cellular changes that are involved in synaptic plasticity. This section is only intended to give the reader an understanding of how chronic use of addictive drugs may interfere with molecular and cellular processes in order to produce the psychological behaviours characteristic of addiction. For a more detailed discussion of synaptic plasticity in addiction, see Kauer and Malenka (2007).

The most widely studied and best understood form of LTP or synaptic plasticity is NMDA<sub>R</sub>-dependent LTP. The co-occurrence of NMDA<sub>R</sub> activation due to presynaptic glutamate release while the post-synaptic membrane is significantly depolarised sets off a signalling cascade that strengthens the synaptic connection (see epigenetic changes below). The activation of the NMDA<sub>R</sub> allows calcium to enter the postsynaptic neuron. This triggers the intracellular signalling cascade that results in an increase in the number of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA<sub>R</sub>) in the post-synaptic membrane. This signalling cascade also produces morphological changes in the neuron that appear to be essential for the LTP of the synapse. This change in the synapse allows a form of information (whether an experience of an event or a learned response) to be encoded in the brain. The process of LTP is best captured in the phrase: “neurons that fire together, wire together”. The molecular mechanisms that underpin NMDA<sub>R</sub>-dependent synaptic

plasticity are depicted in Figure 8. These synaptic changes also involve a number of fundamental cellular processes, such as intracellular signalling, gene regulation and expression, protein synthesis and trafficking, membrane organisation and excitability, and neuronal morphology (see Figure 7.).

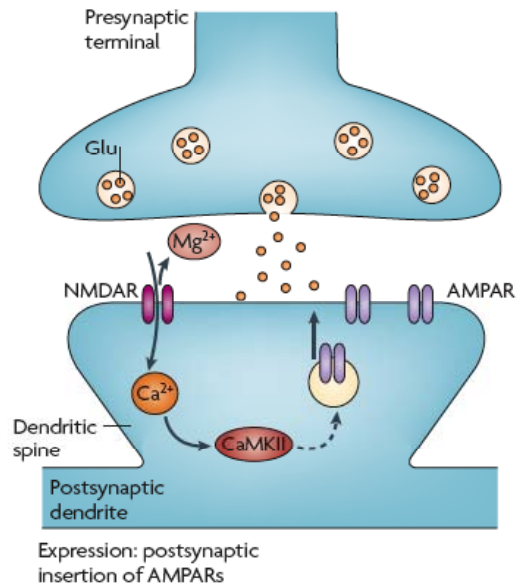


FIGURE 8. NMDA<sub>R</sub>-DEPENDENT LONG-TERM POTENTIATION

n-methyl-d-aspartate receptor (NMDA<sub>R</sub>)-dependent long-term potentiation (LTP) has been observed in glutamatergic neurons in many different brain regions. It is dependent upon the co-occurrence of postsynaptic NMDA<sub>R</sub> activation during significant membrane depolarization, which then initiates internal signalling molecules, such as calcium/calmodulin-dependent protein-kinase II (CaMKII). These signalling molecules result in the insertion of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA<sub>R</sub>) into the postsynaptic membrane. There are several other types of synaptic plasticity that have been observed. They are beyond the scope of this report to discuss here, but they all involve a network of complex molecular and synaptic changes, similar to those depicted in the figure. See Kauer and Malenka (2007) for a more complete discussion.

The association between synaptic changes and learning and memory was first described in hippocampal neurons, a region that is important in remembering the details of events (declarative memory). It has been argued that addiction is a form of pathological learning and memory (Kelley, 2004; Hyman, 2005; Hyman et al., 2006).

However, it is becoming apparent that the plasticity of LTP and the complementary LTD are basic molecular processes that occur at other synapses throughout the brain, including the mesolimbic reward pathway, and cortical regions (Kauer and Malenka, 2007). The strengthening or weakening synapses in these regions are associated with a wide variety of cognitive functions.

There is now increasing evidence that the processes involved in synaptic plasticity are involved in the maintenance of a number of addictive behaviours. These processes may provide the molecular mechanisms for the neuroanatomical changes that underpin the behaviours that are characteristic of addiction, such as craving, impaired impulse inhibition and relapse (Kauer and Malenka, 2007). Many of the molecules implicated in LTP and LTD have been shown to be involved in the synaptic plasticity due to drug abuse (Kelley, 2004). Blocking NMDA<sub>R</sub>s, for example, prevents the development of addictive behaviours and synaptic changes in animal models of addiction (Kauer and Malenka, 2007). Many of the signalling molecules mentioned earlier are able to influence the strength of glutamate signalling by the induction of the plastic changes at the synapse that underpin long term neuroadaptations (for example, see Featherby et al. (2008), who shows that corticosterone influences AMPA-regulated changes in signalling).

Drugs of abuse can co-opt synaptic plasticity mechanisms in the neural circuits involved in reward and reinforcement (Kauer and Malenka, 2007) in the mesolimbic dopaminergic reward pathway, including the VTA and the NAcc. Other limbic regions, including the prefrontal cortex, also undergo neuroadaptations that can result in addiction. Synaptic plasticity within the VTA may be responsible for both the initial acute responses to drugs of abuse and the long-term adaptations in regions that are innervated by the dopaminergic neurons of the VTA (Volkow and Fowler, 2000; Kauer and Malenka, 2007).

The development of more deeply ingrained addictive behaviours in response to chronic drug use over longer periods of time may be the result of plastic changes in downstream regions, such as the NAcc and other limbic regions. Synaptic plasticity within these regions results in the formation of strong, long-lasting associations between the reinforcing effects of drugs and the various cues, both external and internal, that are connected with drug use (Calabresi et al., 2007). It is these long-lasting changes that appear to underlie the experience of drug craving, the motivation



to use drugs, and relapse to drug use on re-exposure to cues associated with drug use or when put under stress.

By identifying the molecular and cellular changes that maintain addiction, it is hoped that it will be possible to develop novel pharmacological drugs that reverse or reduce these changes and thereby increase our ability to treat and possibly prevent addiction (Calabresi et al., 2007). This raises the interesting possibility that a drug may be developed that enables individuals to use drugs, such as heroin, without developing addiction (Nutt and Lingford-Hughes, 2008). This possibility raises a number of ethical and public policy issues we will discuss in the next section of the report. Next we discuss the molecular genetic changes in the cell that may mediate these synaptic changes.

### **Epigenetic Changes in Addiction**

In recent years there has been increasing interest in understanding how environmental factors, such as stress, aggression and drug abuse, regulate the expression of genetic information. The study of non-genetic factors that alter the expression of genes is referred to as **epigenetics** (Tsankova et al., 2007). Research shows that certain environmental events (epigenetic factors) can interfere with gene expression by physically altering the ability of transcription factors to bind to the DNA (deoxyribonucleic acid) and transcribe a given gene. The effect of these changes is to alter gene expression without actually affecting the genetic code in the cellular DNA.

In the cell nucleus, chromosomal DNA is tightly coiled around structures called histones, which can prevent or inhibit the transcription of a given gene. Epigenetic events can cause chemicals to bind to the chromosome, a process called **chromatin remodelling**. This can interfere with gene expression by: 1) **methylation** (i.e. addition of methyl groups to DNA) that inhibits gene expression, or by 2) **acetylation** (e.g. addition of acetyl groups to the histone that loosen DNA folding) that allows easier transcription and thereby facilitates gene expression. Research is beginning to uncover epigenetic changes produced by drug abuse that may produce plasticity at the synapse outlined above that mediate addictive behaviours. One such change involves the regulation of the molecule, *cyclin-dependent kinase 5 (Cdk5)* which we discuss below.

The chronic use of addictive drugs appears to produce a number of changes in cellular morphology. It can increase dendritic branching and the formation of dendritic spines (Robinson and Kolb, 2004; Maze and Nestler, 2011), the specialised regions on the dendrites that enable the formation of strong synapses and allow for quick synaptic signalling. These changes can play an important part in LTP and synaptic plasticity described above. The chronic administration of cocaine to rats increases dendritic branching. Nestler's group found that inhibition of *Cdk5* reduced the effects of cocaine on dendritic branching (Nestler, 2004). Cocaine-dependent rats also had a four-fold increase in acetyl groups bound to the histone at the *Cdk5* gene. Chronic cocaine use is therefore understood to cause epigenetic modification of *Cdk5* expression, thus increasing *Cdk5*-dependent increases in synaptic plasticity (Nestler, 2004).

One of a number of genes that undergo epigenetic modification is brain-derived neurotrophic factor (BDNF). Researchers have also elucidated a number of the molecular mechanisms that are involved in epigenetic processes. For a full review, see Renthal and Nestler (2008). These modulations of gene expression could be the molecular mechanisms by which drug use is able to produce neuroadaptations (e.g. changes in connectivity at the synapse) that are associated with relapse and may make addiction such a persistent problem. These molecules provide another potential target for pharmacological interventions to reduce and possibly reverse the effects of drug use.

## **Brain Imaging Studies of Addiction in Humans**

Animal studies have provided a detailed understanding of the neurocircuitry and pharmacology of addictive drugs but the relevance of these results to human addiction needs to be tested. Human clinical studies are also necessary to assess the safety and efficacy of new treatments of addiction suggested by animal models of addiction. Until recently, the existence of a reward pathway in humans had to be largely inferred from animal studies, with the exception of a small number of studies of the effects of accidental lesions in human subjects. This situation has changed with the advent of non-invasive imaging technologies that enable scientists to more directly verify that comparable changes occur in the analogous regions of the brains of addicted humans.

Neuroimaging studies also enable researchers to investigate aspects of human addiction that cannot be studied in animal models, such as subjective reports of craving. Craving is a potent trigger of relapse to drug use the existence of which can only be inferred in animal studies. The use of subjective reports of craving are not without their own concerns (Stritzke et al., 2004): “craving” is an extremely broad term that can be refer to a number of different cognitive or emotional states. It is also unclear how individuals’ reports of craving correlate with neurophysiological changes. Despite these concerns, craving is widely regarded as a central feature of addiction.

Many of the most significant results from animal studies have been replicated in human addiction. For example, neuroimaging technologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have shown that addictive drugs produce large increases in DA in the NAcc that are correlated with subjective reports of drug “high”, a finding that could not be obtained in animals. Neuroimaging also suggests that chronic drug use in humans dampens activity in the reward pathway, producing an enduring down-regulation of DA receptors in the NAcc (Volkow and Fowler, 2000; Heinz et al. 2005; Fehr et al. 2008; Sevy et al. 2008; Volkow et al. 2009; Cosgrove, 2010). See Figure 9. It is yet clear whether these changes are the result of chronic drug use, as Volkow suggests, or a state that drives vulnerable individuals to use drugs (Garvan et al. 2007). Large prospective studies that are now underway in Europe (IMAGEN) may provide an answer to these questions (Schumann, 2007).

Drug dependent individuals also report significant increases in craving following exposure to stimuli or cues associated with drug use (e.g. pictures of drugs, drug paraphernalia) (Childress et al., 1993). Imaging studies have shown that drug-paired cues can increase DA activity (Volkow et al., 2006; Wong et al., 2006). Neuroimaging of drug dependent individuals who are exposed to drug-related cues suggests that cue-induced relapse is mediated by changes in the amygdala, as is the case in animal studies (Grant et al., 1996; Childress et al., 1999; Kilts et al., 2001; Kilts et al., 2004).

Some of the most important discoveries in neuroimaging studies of human addiction have been the identification of neurobiological changes in decision-making and executive control. The ability to directly visualise the brain of addicted individuals has identified changes in multiple brain systems that may explain “loss of control” and “compulsive drug” taking. These changes may also explain why abstinence is difficult

to achieve and why relapse so often occurs after long periods of abstinence. In the next section, we briefly review the evidence from neuroimaging studies that are pertinent to these aspects of addiction.

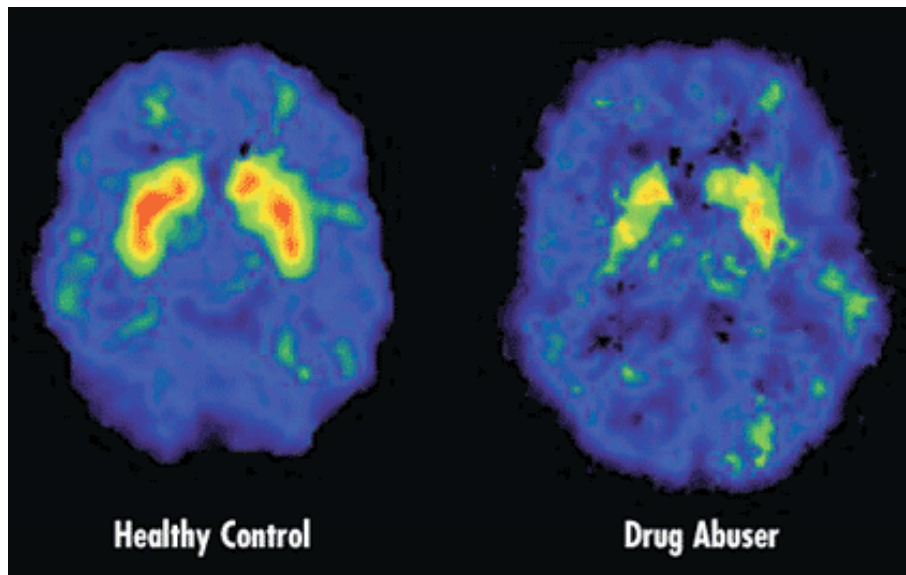


FIGURE 9. DECREASED DOPAMINE RECEPTORS DUE TO DRUG ABUSE

While initial drug use produces large increases in dopamine activity, chronic drug use eventually leads to a significant reduction in dopamine activity. The stimulant, methamphetamine abuse produces significant decreases in the density of dopamine receptors in the striatum. Such persistent changes in dopamine signalling are thought to explain why individuals with an addiction become so motivated to consume drugs. (Source: NIDA website, adapted from Volkow et al. (2001)).

### ***Compulsion, Craving and Inhibitory Control***

In recent years, neuroimaging researchers have studied changes in the frontal cortex of addicted individuals, particularly the *orbitofrontal cortex* (OFC) and the *anterior cingulate gyrus* (aCG). These regions are hypothesised to be involved in craving and compulsive drug taking and loss of control over drug use, respectively (Jentsch and Taylor, 1999; Yucel et al., 2007; Feil et al., 2010). The OFC provides internal representations of the saliency of events and assigns values to them. This allows an individual to compare the likely consequences of pursuing different goals

(Schoenbaum et al., 2006). The aCG is involved in the inhibition of impulses to act (Yucel et al., 2007), and in the control of attention (Bush et al., 1998).

Imaging studies have shown that reduced dopamine activity in the NAcc is correlated with changes in activity in the OFC and the aCG (Volkow and Fowler, 2000; Goldstein and Volkow, 2002; Volkow and Li, 2004). Exposure to drugs and drug-related cues dramatically increases activity in the OFC and aCG of addicted individuals (Daglish et al., 2001) (see Figure 10.). The increased metabolic activity in the OFC and aCG of active drug users in response to dopamine is thought to partly explain craving. Addicts show increased activation in the OFC when presented with drug cues, memories of past drug experiences or their drug of addiction. The degree of activity in the OFC and aCG is correlated with subjectively reported drug craving (Volkow and Fowler, 2000; Daglish et al., 2001; Volkow et al., 2004b; Risinger et al., 2005). There is also evidence that drug-related stimuli are subject to enhanced processing very early in the process of perception, perhaps even at the level of primary sensory cortex (Daglish et al., 2003).

Changes in dopamine activity in the OFC also accompany the process of withdrawal (Volkow et al., 1991). As an addicted drug user undergoes detoxification, metabolic activity within the OFC changes from extremely high to extremely low. Exposing addicts during withdrawal to either their drug of choice or drug-related cues produces hyperactivity within the OFC that is correlated with self-reported drug craving. OFC-induced craving appears to be responsible for the compulsion to take drugs. These changes within the OFC can persist into abstinence, explaining why many abstinent drug users report continued urges to use drugs and relapse in response to drug-related cues.

### ***Executive Control and Cognitive Impairment***

To the lay person, addicts' continued use of drugs despite adverse consequences seems self-evidently to reflect impaired *executive control*, that is, an impaired ability to reason and make rational decisions. It is only recently, however, that the neural centres of executive control and cognitive decision-making have been implicated in addiction (Bechara, 2005; Garavan and Stout; 2005 Goldstein et al., 2007).

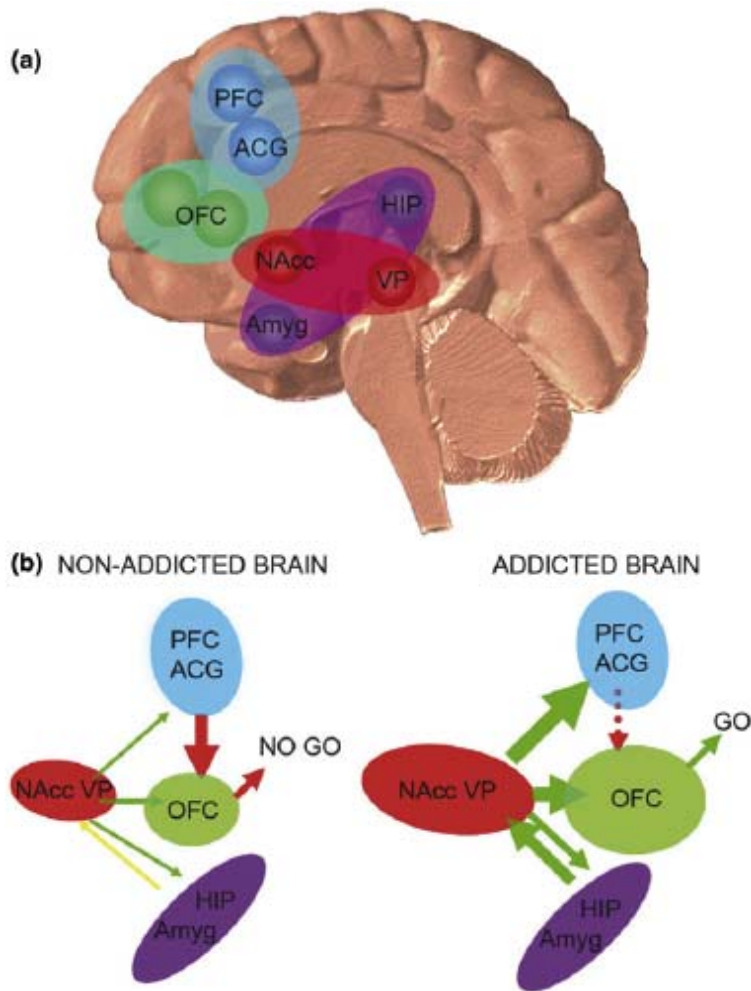


FIGURE 10. HYPOTHESISED PLASTIC CHANGES IN THE NEUROANATOMY OF ADDICTION

This is a schematic diagram of the neuroanatomy of addiction, which depicts the plastic changes that result from chronic drug abuse and produce addiction. (a) The sagittal (side-on) view of a brain depicting four circuits that are postulated to have key roles in addiction: (1) the prediction of reward and pleasure (red) involve the nucleus accumbens (NAcc) and ventral pallidum (VP); (2) memory and learning (purple), occur in the amygdala (Amyg) and hippocampus (HIP); (3) motivation, drive and salience evaluation (green) occur in the orbitofrontal cortex (OFC); and (4) cognitive control (blue), in charge of restraining cravings, located in the prefrontal cortex (PFC) and anterior cingulate gyrus (ACG). (b) A hypothetical model of addiction. Chronic drug use increases the salience value of a drug (red) and its associated cues (purple) in addiction (right) when compared to the non-addicted brain (left), whereas the strength of inhibitory control is weakened (blue), setting up the stage for an unrestrained motivation (green). This results in the repeated use of drugs despite the consequences it causes, and attempts to stop. (Source: Baler and Volkow (2006)).

The decision to continue to use drugs involves the selection of goals from a range of choices. The ability to represent goals, value and select different sequences of actions is thought to depend on the maintenance of goal representations within the prefrontal cortex (PFC) (Roesch and Olson, 2004; Rolls, 2004). Hyman (2005, 2006) has suggested that the ability to update information within the PFC, select new goals and avoid the compulsive repetition of a particular behaviour is controlled by dopamine release. He hypothesises that changes in dopamine signalling affect our ability to make new goals or choose different behaviours. This appears to be confirmed by computational studies of dopamine firing that suggest that addictive drugs provide a potent signal that disrupts normal dopamine-related learning in the PFC (Schultz et al., 1997; Schultz, 2006). Natural rewards, with relatively low dopamine signalling, may fail to open the PFC gate, powerfully biasing the behaviour of addicts towards drug use and away from normal everyday activities. This hypothesis is supported by neuroimaging studies. Cues that predict drug availability take on an exaggerated incentive salience or motivation because of dopamine release in the nucleus accumbens and prefrontal cortex. As a result, drug-seeking behaviour is strengthened by dopamine effects in the prefrontal cortex (Robbins and Everitt, 1999; Berke and Hyman, 2000; Berke, 2003).

In addition to increased motivation to use drugs, addicted individuals often have cognitive impairments that prevent them from either recognising the consequences of their drug use or inhibiting their impulses to use drugs. Recent imaging research has highlighted changes in the dorsolateral PFC and the aCG that seem to prevent addicted individuals from either considering options other than drug use or inhibiting impulses to use drugs (Garvan et al. 2007; Feil et al., 2010). The results of neuroimaging studies are supported by neurocognitive tests that have found impaired attention and reduced executive control in addicted individuals (Bechara et al., 2001; Fillmore, 2003; Hester and Garavan, 2004). There is evidence that drug users have impairments in the OFC region that is involved in attributing emotional value to outcomes. In gambling tests, cognitive tasks which assess the ability of individuals to refuse large, immediate rewards with even larger losses, in favour of smaller, but long-term benefits, drug users perform at worse than healthy controls, but better than patients with OFC damage (Rogers, 1999 #2909; Bechara, 2005; Garavan and Stout, 2005; Goldstein et al., 2007). There is also evidence that drug users are less able to activate this brain region while undertaking the gambling task (Ersche et al., 2005). It is not possible to fully review this vast area of research. Interested readers are directed to a recent reviews by Yucel and Lubman (2007) and Feil et al. (2010).

Several commentators have argued that decision-making includes affective and visceral processes in addition to more rational cognitive processes of analysing and balancing different action options (Paulus, 2007). Similarly, there has been an increasing emphasis of the role that *interoception*, the awareness of sensations of the body, plays in driving us towards choosing certain actions (Damasio et al., 2000; Craig, 2002). The insular cortex (IC) appears to be central in bodily perceptions or feelings. In the case of addiction, the IC may play a key role in explaining why cravings have the ability to capture or steer our thinking and acting. We discuss the role of interoception in drug craving next.

### ***Representing Bodily Urges***

The ability to represent the internal state of the body, or *interoception*, is important for an organism to maintain *homeostasis* – the process which keeps the body functioning in a stable, generally productive condition (Damasio, 1999). Interoception is also critical in shaping or influencing the choices we make (Damasio et al., 2000; Craig, 2002). It is important in helping to decide what is required in a given situation to suit the body's needs (Paulus, 2007). These states are often referred to as *affective states*, because we are affected by them. They are also considered to be emotional states.

The insula – a region of cortex that lies at the intersection of the frontal, temporal and parietal lobes – has been implicated in interoception. The insula receives inputs from the thalamus that convey information about the emotional and homeostatic state of the body. The insula also has connections to several cortical regions, including the sensory and association cortices, the OFC and aCG, and the brainstem and limbic system, including the amygdala, hypothalamus, NAcc and striatum. These dense connections enable the insula to link information from the body's emotional centres and conscious feelings from cortical regions. The insula is therefore understood to be involved in the conscious perception of the physiological state of the body. It sends this information to prefrontal cortical regions to influence decisions on what to do (Everitt and Robbins, 2005). It also plays a role in emotions and autonomic responses.

Given the role of the functions subserved by the insula, it is not surprising that the insula appears to play a critical role in addiction (Contreras et al., 2007). Animal studies suggest that the insula may represent internal body states, such as craving,



withdrawal, or the desire to take drugs, that are triggered by drug-associated cues (Kilts et al., 2001; Bonson et al., 2002). The role of the insular cortex in the experience of drug craving is seen in neuroimaging studies which show that the insula is active during cue-induced craving in addicts, and that its level of activation is correlated with subjective reports of drug craving (Contreras et al., 2007).

The awareness or conscious experience of the body's response to drugs is critical in the maintenance of addictive behaviours. The experience of cravings for drugs is a potent motivator for addicts to use drugs. Inactivation of the insula prevents drug seeking in rats (Contreras et al., 2007). A recent study also showed that individuals who had lesions in the insula cortex were able to quit smoking easily and were less likely to relapse (Naqvi et al., 2007). Damage to the insula did not increase the likelihood of quitting but it increased the success among those who tried, and reportedly reduced their desire to smoke. The role that interoception plays in the choices we make, and the role that the insula plays in this process in addiction is receiving increasing attention in addiction neuroscience (Verdejo-García and Bechara, 2009). Targeting these regions may lead to new medical treatments. It may also help clinicians to develop psychotherapies that attempt to overcome these changes in cognition.

## **Vulnerability to Addiction: Genetic and Psychological Factors**

This section briefly summarises research on two related topics: studies of twins and genetic association studies which indicate that genetic factors (including individual differences in drug metabolism and neurotransmitter responses to drug effects) contribute to differences between people in their vulnerability to addiction; and neuropsychological and neuroimaging research which suggests that genetic differences in cognitive performance may influence vulnerability to addiction.

### ***Genetic Susceptibility to Addiction***

Familial studies have consistently shown that addiction “runs in families” (Merikangas et al., 1998), suggesting that there is a substantial genetic contribution to addiction vulnerability (Ball and Collier, 2002; Ball et al., 2007). Addiction is among the most heritable of the complex psychiatric disorders (Goldman et al., 2005), despite the facts that an individual must engage in drug use for the genetic predisposition to be

expressed, and that the use of drugs is therefore influenced by personal choices and social policies. Evidence from twin and adoption studies suggest that 40-60% of the risk of developing substance abuse disorders is due to genetic factors, with the percentage depending on the substance (Uhl et al., 2004; Li and Burmeister, 2009 ). Some studies suggest that the genetic contribution to addiction to some substances, such as cocaine, may be over 70% (Goldman et al., 2005).

An individual's inherited genetic make-up can influence addiction risk in a number of ways. Genes may affect: behavioural traits that influence an individual's willingness to try drugs (e.g. risk-taking behaviour, impulsivity, novelty seeking); the way in which individuals respond to particular substances (drug metabolism, absorption and excretion, and activity or sensitivity to drugs); or the likelihood of developing problem use or dependence if they use drugs (e.g. by affecting how rewarding they find the effects of particular drugs) (Rhee et al., 2003). This suggests two broad types of genetic predispositions to addiction: (1) genetic profiles that make some individuals more likely to find the acute effects of drugs rewarding and (2) genetic profiles that make individuals more or less susceptible to developing addiction if they do use drugs. Significant environmental events, such as adolescent physical or sexual abuse, can interact with genetic susceptibility to increase the risk of developing psychiatric disorders (Nestler, 2000; Caspi et al., 2005; Ball et al., 2007; Ball, 2008). There is convincing evidence that both genes and environment play a significant role in the development of addiction (Ball et al., 2007; Ball, 2008).

Despite the strong evidence of genetic contributions to addiction vulnerability, attempts to reliably identify specific addiction susceptibility genes have been disappointing to date. Large scale linkage and association studies have identified numerous promising candidate genes that confer vulnerability to addiction (Ball and Collier, 2002; Tyndale, 2003) but few of these alleles have been consistently replicated and the associations for those genes that have been replicated are modest (Tyndale, 2003). Most of the candidate genes identified so far are associated with the activity of dopamine and the dopaminergic system, dopamine receptors and transporters,<sup>12</sup> or with proteins that influence the pharmacological activity or metabolism of addictive drugs.

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<sup>12</sup> For example the catechol-O-methyl transferase (COMT) and dopamine receptor 2 (D2).

The strongest evidence for vulnerability or resilience to addiction concerns a gene, aldehyde dehydrogenase 2 (ALDH2), which encodes a variant of the enzyme involved in the metabolism of ethanol (Thomasson et al., 1991; Chen et al., 1999). The ALDH2 gene encodes for a less active variant of the metabolic enzyme. Individuals who are homozygous for the ALDH2 allele (i.e. have two copies) are more likely to experience facial flushing, nausea, and headaches if they drink alcohol. A high prevalence of these alleles is thought to explain the lower incidence of alcoholism in some East Asian populations (Nestler, 2000).

Addiction is a complex disorder so there are likely to be many genes associated with addiction risk, most of which make a small individual contribution to risk (Khoury et al., 2003; Tyndale, 2003; Hall et al., 2004a; Khoury et al., 2004; Ball et al., 2007). The most plausible hypothesis is that there are a substantial number of genes that are involved in the initiation, adoption, persistence and cessation of drug abuse, each of which carry a small relative risk (Lerman and Berrettini, 2003). The effects of these types of genetic profiles will depend on environmental cues and triggers, such as stress, opportunity to use different drugs, peer and parental drug use and so on.

Improved understanding of genetic contributions to the development of addictive disorders raise the possibility that we can prevent the onset of drug use and addiction in high risk individuals. By identifying those who are genetically vulnerable to addiction, it may be possible to prevent addiction by vaccinating individuals against the rewarding effects of drugs of abuse. Psychopharmacotherapies could also be tailored to individual's genomic vulnerabilities (pharmacogenomics and pharmacogenetics) to allow more effective and efficient addiction treatments. By identifying genes and genetic products involved in the development of addiction, such as initiation, problem drug use, tolerance, withdrawal, dependence, craving and relapse, it may also be possible to develop treatments aimed at an individual's genetic and neuropsychological vulnerabilities.

### ***Vulnerabilities to Addiction: A Confluence of the Genetic and the Social***

In addition to genetic susceptibilities, there are social factors that make some individuals more likely to develop an addiction than others. These include socio-economic background, exposure to parental drug use, peer drug use and early exposure to drugs, physical or sexual abuse, poor performance at school, and mental

disorders such as conduct disorder and anxiety and depressive disorders that develop during adolescence (Hawkins et al., 1992).

Both genetic and environmental susceptibilities to developing addiction are mediated by neuropsychological changes in the brains of drug users. Genes implicated in addiction are thought to produce changes in the structure or function of specific neural circuits during development that affect an individual's responsiveness to the effects of drug use. The fact that the addiction liability of different drugs (i.e. their neuropharmacological properties) correlates with the genetic risk of addiction suggests that genetic vulnerabilities to addiction are mediated by neurobiology (Goldstein and Kalant, 1990; Goldman et al., 2005). Environmental stressors and early exposure to drug use, particularly during adolescence and early development, can also have significant neuropsychological effects that leave individuals vulnerable to substance abuse or addiction (Volkow and Li, 2005b).

Brain imaging studies suggest that vulnerability may be due to: a decreased sensitivity to natural reinforcers; disrupted activity in control circuits; sensitivity to conditioned drug stimuli; responses of motivation/drive circuits to drugs; and neurobiological factors involved in the modulation of these circuits (Volkow and Li, 2004). These changes are thought to be mediated, at least in part, by changes in dopaminergic signalling.

As already discussed, differences in dopamine circuits are thought to underlie individual differences in responsiveness to drug effects that, in turn, influence vulnerability and resilience. This variation in responsiveness to drugs is largely due to genetic make-up. Dopamine activity is also affected by environmental events since stress can increase dopamine release in the NAcc (Koob, 1999b) and affect levels of the dopamine receptors (Papp et al., 1994). Studies in primates show that dopamine activity is also affected by position in the social hierarchy (Morgan et al., 2002).

Dopamine function also influences predispositions to self-administration of drugs in animals. Genetic manipulation of the dopamine receptor 2 (D2) markedly affects drug self-administration. Low D2 levels might predispose an individual to use drugs to compensate for decreased activation of the reward circuit, whereas high D2 levels might be protective. Genetic up-regulation of D2 receptors in rats reduces alcohol consumption, suggesting a target for treatment with drugs or environmental manipulations that increase D2 expression. The fact that many non-addicted

individuals also have low D2 levels suggests that low D2 levels only predispose to addiction.

Other behavioural traits or cognitive capacities unrelated to the dopaminergic reward pathway are also thought to influence vulnerability to addiction. Functional MRI imaging studies of individuals who are impulsive find differences in the corticolimbic behavioural arousal and control circuits that are affected by addiction (Brown et al., 2006). Cognitive control is another relatively stable trait that is an important predictor of life success that plays an important role in the development of addiction (Eigsti et al., 2006). Individuals with disorders of impulsivity such as attention deficit hyperactivity disorder (ADHD) or cognitive impairment are more likely to develop substance abuse disorders (Lynskey and Hall, 2001). There is also a high incidence of substance abuse among individuals with anxiety or depressive disorders in whom drug use may be a failed attempt to self-medicate dysphoric (unpleasant) symptoms (Khantzian, 1985). Chronic drug use can also produce anxiety and depressive disorders. The causal relationship between addictive and affective disorders can probably occur in both directions, and to varying degrees in different individuals. These disorders may also share a number of common causes.

Epidemiological and neuropsychological research supports the hypothesis that the brains of adolescents and young adults may be developmentally more vulnerable to developing addiction if they use drugs than those of older adults (Lubman, Yucel and Hall, 2007, Volkow and Li, 2005c). Mesocortical tracts that are involved in cognitive processing, executive control and motivation are not fully developed in the adolescent brain (Sowell et al., 2004).<sup>13</sup> In fact, the PFC does not fully mature until the early 20's (Gogtay et al., 2004). The neuroanatomical connections between the amygdala and PFC – the circuit responsible for cognitive control over emotions – are not fully developed until adult life (Cunningham et al., 2002). While the neuroscientific evidence to support this hypothesis is still mounting, it is strengthened by robust epidemiological evidence of the risk of adolescent alcohol consumption.

These hypotheses suggest two predictions. First, as the regions of the brain responsible for impulse inhibition and reasoning about consequences are not fully developed, adolescents are more likely to engage in risky behaviours such as drug use. They find it more difficult to inhibit impulses, are more likely to engage in novelty

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<sup>13</sup> Myelination of the mesocortical tracts, a cellular process that enables neurons to signal quickly and efficiently, is not complete in the adolescent brain.

seeking, and suffer from a temporal myopia that prevents a full appreciation of the future consequences of their behaviour (Volkow and Li, 2005b). Secondly, the developmental immaturity of the adolescent brain means that adolescents may be particularly vulnerable to the neurobiological changes that occur as the result of chronic drug use. Neuropsychological changes at such a developmentally sensitive period can reduce the individual's cognitive capacities in overcoming addiction. These hypotheses, which remain to be tested, could explain why epidemiological studies show that people who engage in substance abuse in early adolescence are more likely to develop addiction and less likely to recover than those who delay drug use until early adulthood.

## **Translational Research in Addiction Neurobiology**

A significant challenge in neuroscience research of addiction is research translation: turning new drugs that look promising in preclinical animal studies into effective treatments for addiction that reduce drug use and harm (Koob et al., 2009). This requires: regular dialogue between addiction neurobiologists and addiction specialists to identify promising new treatments; and the existence of the necessary expertise, funding and clinical research infrastructure to conduct the controlled clinical trials that are needed to assess the efficacy and safety of potential new drug treatments for addiction.

There are substantial technical and practical challenges to be overcome in conducting the clinical trials to provide the evidence needed to approve the use of a new drug and then funding its delivery to persons with addictions (Woody and McNicholas, 2004). Technical difficulties arise from differences between tightly controlled laboratory experiments on animal models of drug self-administration and the use of addictive drugs by humans. There have been numerous findings in animal models that were not replicated in addicted humans (e.g. preclinical trials of drugs such as dopamine antagonists and antipsychotics; we discuss these further in the chapter on Treatment of Addiction). Drugs can also have significant side-effects in humans that prevent the use of treatments that are very effective in animal models. And unlike animals, addicted humans can choose not to comply with treatments or may use therapeutic drugs in ways other than those intended.

Pharmaceutical companies have not traditionally invested in addiction research (McLellan et al., 2000). The companies do not see the market for addictive drugs as being a large and profitable one in part because of the limited capacity of addicted individuals to pay for their treatment and in part because of the regulatory challenges that have to be overcome in testing, registering and then using agonist drugs to treat addiction. One consequence of this lack of interest is that the US government (via the National Institute on Drug Abuse) has often funded research on the development of new drugs deriving from neurobiological research on addiction (such as naltrexone, buprenorphine, and cocaine and nicotine vaccines) (Kosten and Kranzler, 2004). Even when promising new drugs have been developed, the capacity of the addictions field to undertake large scale controlled clinical trials has been limited by the lack of a strong research tradition in the field. And when drugs have been approved for clinical use there may be major challenges in having them adopted by the specialist addictions field or primary care physicians (Thomas and McCarty, 2004).

There are also societal and political sensitivities to consider. If a safer alternative to alcohol were developed, it would likely face significant challenges in ever getting to market. Any agent that produced intoxication, disinhibited behaviour and impaired cognitive and motor function without producing addiction or physical damage associated with alcohol is unlikely to be granted regulatory approval for general sale. A similar difficulty has emerged in the evaluation of smokeless tobacco products in countries where they are restricted, such as in Australia (Gartner and Hall, 2008). We discuss the ethical and public policy implications of such developments below.

## Neurobiological Treatments of Addiction

Advances in genomic and molecular biology, such as the ability to clone and sequence receptor subtypes, transporters and endogenous agonists, have the potential for significantly increasing our ability to develop novel and specific treatments for addiction to a variety of substances. Sites of action for many drugs of abuse have been identified. For most of these drugs, the molecular sites of action are neurotransmitter receptors and transporters that regulate neurotransmitter activity at the synapse (Iverson et al., 2007). Drugs of abuse often work by mimicking the effect of endogenous neurochemical signalling. For example, heroin produces its effect by mimicking the action of endogenous opioids (e.g. endorphins and enkephalins) (Nutt, 1996).

These discoveries have enabled scientists to identify and specifically target relevant receptor or transporter sites with drugs that either block (antagonists) or facilitate (agonists) activity at this site. Antagonists are typically those drugs which block the action of the addictive drug (e.g. naltrexone blocks the effect of heroin), while agonists are drugs which mimic the effect of the addictive drug (e.g. methadone for heroin dependence). The use of opioid agonists in substitution treatments and of opioid antagonists in relapse prevention are discussed in greater detail below.

The use of genetic manipulation techniques in animal models has also greatly increased our understanding of psychopharmacology of addiction. Genetic manipulation in a developing animal allows researchers to observe the effect of increasing (e.g. over-expression mutants) or blocking (e.g. transgenic knockouts or dominant-negative mutants) the activity of a specific molecule. These techniques help us to understand the role that these molecules play in the onset and progression to addiction, and in affecting responses to drug use; information that assist researchers in discovering potential new therapeutic agents.

The advent of psychopharmacological neuroimaging techniques has also been invaluable in understanding the impact of functional changes within humans. Neuroimaging of addiction in humans has been critical in linking developments in animal research with our understanding of addiction in humans. By unravelling the various pharmacological processes that underpin the phenomena of addiction, these



discoveries have provided a number of novel and promising sites for intervention. These discoveries also point towards the possibility of a more rational (and less serendipitous) approach to developing addiction treatments that are based on more comprehensive theories of the brain mechanisms underlying addiction (Nutt, 1996; Nutt et al., 2007a).

Pharmacological treatments of addiction can be classified into those that:

- Block the target drug from binding to its site of action
- Ameliorate the symptoms of withdrawal
- Reduce the impact of drug craving or relapse, either by: interfering with the central dopaminergic response to addictive drugs, or other neurotransmitter systems related to the reward pathway (e.g. opioids, cannabinoids, glutamate/GABA, and the stress response), and
- Minimise the harmful effects of drug abuse.

## **Pharmacological Treatments that Block Drug Binding**

The traditional approach to pharmacological treatment of addiction involves using drugs that interfere with or block the site at which the drug of addiction acts (e.g. mu-opioid receptor for heroin). These medications were first developed to treat addiction to opioids, which have generally been the most effective (e.g. methadone, buprenorphine and naltrexone). Whether a similar approach will be effective with other drugs of abuse is an empirical question. Nicotine replacement therapy (NRT) is the most common form of substitution treatment, but is not particularly effective in helping smokers quit, with relapse rates of up to 82%. To date, effective pharmacological treatments of psychostimulant addiction have proven elusive. This may be due to difficulty in directly interfering with the dopaminergic system or possibly because the wrong receptors have been targeted (see below). As alluded to above, it is possible that an approach that works for one type of drug abuse (opiate) will not be effective for another type of drug abuse (stimulant).

All treatments which act by blocking the direct binding of the abused drug fall into one of three categories: (1) agonist; (2) antagonist; and (3) partial agonist. These are described below. A detailed description of treatments for all drugs of addiction is beyond the scope of this report. For a complete review of all available and promising pharmacological treatments of addiction to various drugs of abuse, refer to the clinical guidelines developed by the British Association for Psychopharmacology

(Lingford-Hughes et al., 2004), or a recent review by Nutt and Lingford-Hughes (2008). A brief description of each approach, their potential for effective treatment, as well as their limitations is provided below. A summary of the most common drugs used in the treatment of addiction, and their primary action and application is provided in Table 5. (Lingford-Hughes and Nutt, 2003).

### ***Agonists***

*Agonists* are drugs that act in a similar way on the same receptors as the endogenous neurotransmitter, and often the target drug of abuse, producing similar effects. Agonist treatment was pioneered by the development of methadone treatment for opioid addiction in the 1960's (Dole and Nyswander, 1965). Treatment involves replacing the abused drug with one that is safer and less likely to produce adverse outcomes. Usually this means that it has slower pharmacokinetics (meaning that it will bind for longer). Drugs with longer action and slower onset of effect tend to be less addictive. Agonists also reduce the experience of drug withdrawal, making abstinence from street drugs easier to maintain. Full agonist substitutes, like methadone, also reduce the effects of street drugs making the experience less rewarding. They often also have a stronger affinity for the receptor site, so the substitute drug (e.g. methadone) is not as readily shifted from the receptor site as the abused drug (e.g. heroin).

The aim of treatment is to mimic the actions of the drug of addiction and occupy the receptors providing some protection against the acute adverse effects of the drug (e.g. overdose in the case of heroin addiction). These drugs should also have slow rates of brain uptake and clearance, thereby providing relatively stable and more enduring concentrations of dopamine in the brain (e.g. oral methadone). New formulations of these drugs to provide even longer periods of stable drug release (e.g. months) are currently being developed. We discuss these developments in detail later (see Depot treatments).

The aim of agonist treatments is to replace the unsupervised use of an illicit drug (e.g. heroin) of unknown strength and purity, with a safer, pharmaceutical grade drug (e.g. methadone) in a regulated manner which offers the potential for support and education. Agonist treatments also reduce the incidence of acute adverse effects of drug use, such as overdose and the spread of BBV. Agonists can also prevent or minimise the symptoms of withdrawal, and reduce craving for the drug of addiction,

leading to greater retention in treatment and better treatment compliance. Agonists have a number of social advantages as well, in that they reduce the incidence of drug-related social harm, such as crime, theft and violence.

Agonists are often used in *substitution* treatment programs (see below) in which the aim of treatment is long-term maintenance. The most well known is methadone maintenance therapy (MMT). Agonists may also be prescribed for shorter periods to assist addicts become abstinent by reducing the symptoms of withdrawal. In the latter case, patients are provided with a tapered dose of the drug that is steadily reduced over a number of days until abstinence is achieved.

The disadvantage of agonists is that they have the potential to cause similar harm as the abused drug if they are used in large doses or diverted to the black market and used by drug naïve individuals who lack the tolerance of chronic drug users. Agonist treatments are therefore usually provided under strict controls and restrictions which can make treatment difficult and unattractive (e.g. daily supervised dosing). Also, because agonists produce a similar reinforcing effect to the target drug, they are also addictive (e.g. methadone and buprenorphine for heroin dependence).

While methadone has proven to be successful in treating opioid addiction, it is not without problems. Methadone can be a very sedating drug, which can cause personal and employment problems for some people. An advantage of a partial agonist like buprenorphine is that it is less sedating than methadone, although some patients prefer methadone for this reason. The long-term use of methadone can also lead to adaptive brain changes that increase withdrawal and insomnia, that can last for weeks (Beswick et al., 2003). New research is suggesting that the success of methadone may not be due to a simple mu-opioid receptor occupancy as first thought (Nutt and Lingford-Hughes, 2008). By better understanding the pharmacological action of methadone, it may be possible to develop an effective agonist drug without these negative side effects.

Drug	Primary target	Primary action	Substitution Therapy (e.g. agonists and partial agonists) <sup>14</sup>	Relapse Prevention (e.g. antagonists, blockers)
Opioids	Mu opiate receptors	Mimic brain endorphins, ↑ dopamine	Methadone <i>Buprenorphine</i>	Naltrexone Naloxone Nalmfene <sup>c</sup>
Stimulants				
Cocaine	DAT	↑ dopamine	Dexamphetamine <sup>b</sup> Bupropion <sup>a</sup> <i>D3 ligands (BP-897)<sup>a</sup></i>	DAT blocker (GR12909) <sup>a</sup>
Amphetamine and meth-amphetamine	DAT	↑ dopamine	Dexamphetamine <sup>b</sup> Bupropion <sup>a</sup> <i>D3 ligands (BP-897)<sup>a</sup></i>	D3 receptor drugs <sup>a</sup> D2 blockers (antipsychotics) <sup>e</sup>
Nicotine	Nicotinic ACH receptor	↑ dopamine	NRT Snus <i>Varenicline</i>	Mecamylamine <sup>a</sup>
Sedatives				
Alcohol	GABA/glutamate	↑ GABA ↓ glutamate	BDZs <sup>b</sup> <i>BDZ partial agonists<sup>a</sup></i>	Acamprosate <sup>d</sup> Naltrexone <sup>d</sup> Disulfiram <sup>d</sup>
BDZs	GABA	↑ GABA	Longer half-life BDZs <i>BDZ partial agonists<sup>a</sup></i>	Flumazenil
Cannabis	CB1 receptor	? dopamine ? opiates	None	Rimonabant
Ecstasy (MDMA)	Serotonin transporter	↑ serotonin	SSRIs <sup>a</sup> <i>Serotonin drugs<sup>a</sup></i>	

BDZs, benzodiazepines; CB1, cannabinoid 1; DAT, dopamine transporter; ACH, acetylcholine; GABA, gamma-aminobutyric acid; SSRIs, selective serotonin reuptake inhibitors.

a. Theoretically effective but no clinical trial data.

b. Controversial, risk of dependency and toxicity.

c. Not available throughout EU.

d. Used to maintain abstinence.

e. Theoretically effective, but not in clinical trials.

TABLE 5. MOLECULAR TARGETS OF DRUGS OF ADDICTION AND PHARMACOLOGICAL APPROACHES (CURRENT AND THEORETICAL). ADAPTED FROM LINGFORD-HUGHES AND NUTT (2003).

<sup>14</sup> Some of the drugs listed in this table are used as substitution or relapse prevention, but cannot be strictly thought of as agonists or antagonists. For example, bupropion increases dopamine activity by blocking the dopamine transporter, not a receptor for an endogenous neurotransmitter, and is therefore not strictly speaking an agonist. Similarly, acamprosate, naltrexone and disulfiram are used as a form of relapse prevention for alcohol dependence, although none are antagonists of GABA: Acamprosate is thought to modulate glutamate function. Naltrexone is an antagonist of all opioids, endogenous and exogenous (like heroin). Disulfiram blocks the breakdown of alcohol at a toxic metabolite causing a very unpleasant reaction to alcohol.

Substitution has not been as successful in the treatment of addiction to cocaine and amphetamines, except for comorbid treatment of ADHD (Lingford-Hughes and Nutt, 2003).<sup>15</sup> This may reflect the importance of changes in other neurotransmitter systems such as noradrenaline. Drugs which increase dopamine can also cause additional health problems, particularly relating to the heart. They can also be abused. Drugs that act as a direct agonist at the dopamine receptor (e.g. bromocriptine) may be theoretically able to be used as substitutes for stimulants, but they also cause nausea, psychotic symptoms and movement disorders.

### ***Antagonists***

*Antagonists* are drugs that bind to a pharmacological site of action, blocking the effects of its agonist, and often the addictive drug itself. Antagonists work by blocking the receptor sites at which the drug of addiction acts (e.g. naltrexone blocks mu opioid receptors for treating heroin dependence), thereby reducing its rewarding effect. Antagonists must also be: safe; have a long half-life (meaning that they remain bound in the brain for long periods, reducing the dose frequency); and possess a strong affinity for the receptor site so that they cannot be easily shifted by the drug of addiction.

Antagonists are most often employed as a prophylaxis against relapse because they block the reinforcing effect of addictive drugs as long as they are taken. This use is referred to as *relapse prevention* (see below). The advantage of antagonists is that they are generally safer than agonists when used as intended; they are not reinforcing or addictive; and they can also reduce acute adverse effects of the abused drug (e.g. overdoses). Their safer profile means that they can be provided with fewer controls and regulations than agonists.

A problem with antagonists is that they can precipitate withdrawal symptoms because they block the activity of the drug of addiction. Thus initiating their use means that addicts have to be detoxified and drug free. Because antagonists do not have any rewarding effect, people often stop taking them and quickly relapse to drug use. In the case of opiates, this can increase the risk of a drug overdose as users are no longer tolerant to opiates. New slow-release formulations of these drugs (e.g.

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<sup>15</sup> Substitution treatment does not imply any particular mechanism of action (i.e. agonist or antagonist). Instead it refers to a medication given to mimic some or all of the effects of the abused drug. As the drugs of abuse can have very different mechanisms of action, a substitute could be an agonist (e.g. methadone) or a re-uptake blocker (e.g. bupropion). Therefore we will not use these the term agonist or antagonist when discussing substitution and relapse prevention for stimulant abuse.

naltrexone implants that reportedly last between 1 and 6 months) have been developed in order to overcome these compliance problems with oral forms of the these drugs (see discussion below).

The most commonly used antagonist is naltrexone for the treatment of opioid dependence. Naltrexone also appears to be effective in reducing alcohol consumption, possibly by blocking the alcohol-induced increase in opioid activity (Srisurapanont and Jarusuraisin, 2005). Flumazenil is an extremely potent benzodiazepine antagonist, but is only effective if given intravenously or subcutaneously. It is also short acting and can cause convulsions. There is also a cannabis receptor (CB1) antagonist available (rimonabant). This drug was initially developed to aid weight loss. It could also theoretically be used to treat cannabis dependence, although more research is required (Nutt and Lingford-Hughes, 2008).

There are no effective antagonist treatments for psychostimulant dependence. Older “typical” antipsychotics are potent dopamine antagonists and block the effects of stimulants, but they cause such marked dysphoria in users that they are not tolerated. Antipsychotics also carry the risk of inducing movement disorders (parkinsonism, dystonia, and tardive dyskinesia). However, there are two drugs being investigated that have shown potential in preclinical trials. Studies in rats show that selective D3 antagonism can reduce drug-seeking (Vorel et al., 2002). Studies also suggest that a D1 antagonist may also reduce psychostimulant consumption.

### ***Partial Agonists***

*Partial agonists* are drugs that bind to the site of action and produce less of a reinforcing effect than full agonists (e.g. buprenorphine for opioid dependence, varenicline for nicotine dependence). Like their pharmacological cousins, partial agonists should ideally have a long half life and a strong affinity for the binding site in order to block the effects of the addictive drug.

The main advantage of partial agonists is that because they have some reinforcing effects they are more likely to retain people in treatment than antagonists. Also, as their agonistic effects are reduced, they are much less likely to cause acute adverse effects, such as overdose. Their safer profile also means that they can be provided under less prohibitive restrictions, with less supervision and with more takeaway

doses.<sup>16</sup> They also provide some protection against the harmful effects of the drug of addiction such as overdose. Because partial agonists, such as buprenorphine, have a lower risk of overdose, much higher doses can be given, ensuring full occupancy of the opioid receptors and effectively blocking the effects of any street heroin use.

Several studies have investigated the potential of using a single large dose of buprenorphine to ameliorate withdrawal symptoms and assist detoxification (commonly referred to as *tapered withdrawal* – see below) (Kutz and Reznik, 2002; Ang-Lee et al., 2006). Also, as partial agonists (e.g. buprenorphine) induce less receptor adaptation, the symptoms of withdrawal are less aversive than the full agonists (e.g. methadone). Buprenorphine produces less of a “stoned” feeling than methadone, which may or may not be advantageous, as we discussed earlier, depending on the individual.

The development of partial agonists to other drugs of addiction have had mixed results. Varenicline, a partial nicotinic agonist, has been shown to be effective in the treatment of nicotine dependence, and research suggests that it may be more effective than bupropion and NRT (Rollema et al., 2007). Studies suggest that it may also be effective in the treatment of other addictions, such as alcohol (Steensland et al., 2007), suggesting that a common nicotinic pathway may be involved in several addictions (Glick et al., 2002). A benzodiazepine partial agonist that produced sedation and reduced the risk of addiction in preclinical trials has failed to have the same effects in human trials (Nutt and Lingford-Hughes, 2008). Researchers held high hopes for partial dopamine agonists (e.g. aripiprazole) for the treatment of psychostimulant addiction but these hopes have also failed to be realised. We discuss the problem of drugs that interfere with the dopaminergic system in detail below.

Despite these positive features, partial agonists do pose a number of risks. As they produce a small agonist effect, they can still produce overdoses, especially when they are used with other CNS depressant drugs like alcohol, and they are often addictive. It is also not clear yet whether partial agonists are as effective in reducing illicit drug use as full agonists (Lingford-Hughes et al., 2004). Partial agonists may not

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<sup>16</sup> There have been increasing problems from injected buprenorphine, particularly when the buprenorphine tablet has been spat out due to poor observation of consumption. There is generally more willingness to allow takeaways of Suboxone: a combination drug that contains both buprenorphine and naloxone.

be as effective as full agonists in reducing the urge to use a drug of abuse in some individuals because of their attenuated rewarding effects.

### ***Duration of pharmacological treatment of addiction***

Pharmacological treatments of addiction may be provided for varying lengths of time, depending on the particular aim of the treatment program. Pharmacological treatments may be used over short periods of time to assist addicted individuals to withdraw from their target drug, called *tapered withdrawal*. Agonists or partial agonists may be used in gradually declining doses over a number of days in order to ease the symptoms of withdrawal from the addicted drug, and to achieve abstinence. This is referred to as *detoxification*.

Agonists or partial agonists may also be used for longer periods in order to encourage less harmful forms of drug use in the short to medium term. The treatment drug is provided as a substitute for the use of the abused drug, and is therefore commonly referred to as *substitution* or *replacement treatment*. When it is seen as a long-term solution, it is referred to as *maintenance* therapy.

Similarly, antagonists may also be used for short periods of time, either to speed up detoxification (e.g. rapid opioid detoxification), although these treatments are uncommon and have not been particularly effective, and can sometimes be dangerous. Antagonists are more often used as a prophylactic against relapse to drug use in the medium to long-term, i.e. as an aid to abstinence. This form of treatment is therefore called *relapse prevention*. Relapse to drug use is a significant and persistent problem in the treatment of addiction. There is significant research underway in order to find treatments that can prevent relapse, or reduce the severity or duration of any returns to drug use.

In reality, intended duration of treatment is often not as clear as this simplified analysis suggests. Often the aim of treatment may be less clearly defined, particularly at the beginning of treatment. The initial aim of treatment will be to stabilise a patient, to provide support and counselling, and to engage them in long-term solutions. Only as treatment progresses are more substantive treatment aims made, many of which evolve as treatment progresses. There is much variability in addiction treatment, according to the drug abused and the individual. Treatment needs to be flexible and cannot be predetermined as a defined and fixed course.



## Pharmacological Treatments to Reduce the Symptoms of Withdrawal

The pharmacological treatment of withdrawal is often referred to as *symptomatic support*. While distressing and intolerable, withdrawal symptoms are rarely life threatening, with the exception of severe alcohol withdrawal. However, treatment of withdrawal symptoms is often a clinical priority because they can lead to a rapid return to drug use. The treatment of withdrawal may be used to supplement pharmacological treatments such as those discussed above, or as the sole form of treatment, particularly where adequate treatment is lacking.

Benzodiazepines are often prescribed for the treatment of alcohol withdrawal to prevent seizures and delirium tremens, by increasing the brain's inhibitory system (via GABA-A). However, benzodiazepine does not reduce the withdrawal symptoms associated with increased glutamatergic activity. This is significant as increased glutamate activity may be neurotoxic. It is hypothesised, for example, to explain cognitive impairments caused by alcohol abuse. Future treatments of alcohol withdrawal may also aim to provide prophylaxis against neuronal loss by decreasing glutamatergic activity. Acamprosate (Campral), a drug already used to treat alcohol dependence appears to reduce glutamate overactivity in animals, and prevent hypermobility and neuronal loss, and so could be used for this purpose in humans (Boeijinga et al., 2004; Staner et al., 2006). Further research is warranted (Nutt and Lingford-Hughes, 2008).

The symptoms of opioid withdrawal can also be quite significant (e.g. tachycardia, severe sweating) and require symptomatic relief. Cessation of opioids in dependent individuals causes a significant increase in noradrenergic activity. Adrenergic agonists, such as lofexidine and clonidine, decrease these symptoms by acting on inhibitory auto-receptors to decrease noradrenaline activity (Maldonado, 1997). They however have no effect on other symptoms of withdrawal that involve the gastrointestinal tract (e.g. nausea or diarrhoea) or insomnia. Despite the clinical significance of drug withdrawal in clinical outcomes, there has been much less research into the development of pharmacological treatments for other drugs of addiction (Nutt and Lingford-Hughes, 2008). More research in this area is warranted.

## **Pharmacological Treatments of Craving and Relapse**

Craving is a particularly salient issue in the long term treatment of addiction. There has been significant interest in anti-craving drugs recently (O'Brien, 2005). However, "craving" is a broad term that roughly describes any strong motivation, urge or desire to take drugs. Our understanding of craving also relies heavily on subjective reports, and may in fact have more than one source. The desire for drugs may be the result of a desire to "get high" (positive reinforcement), to deal with stressful life events or overcome anxiety or dysphoria (negative reinforcement), or simply just a strong urge without a reason or purpose. As we described in the previous section, there are different neural circuits and neurochemicals that have been hypothesized to produce these different types of craving and lead to relapse. Therefore, rather than attempt to simply review the drugs intended to reduce drug craving and relapse, we will discuss drugs that target specific aspects of the circuits that produce cravings.

### ***Dopaminergic Mesolimbic Reward Pathway***

Many researchers have believed that drugs that target the dopaminergic system would also provide effective treatment for addiction. However, an effective dopaminergic treatment of addiction remains elusive. The only exception to this is bupropion, a dopamine transporter inhibitor that is effective in helping some smokers to stop. The question remains not why bupropion works for smoking, but why it does not appear to work for other addictions. It may be that the drugs used so far have targeted the wrong dopamine receptor (e.g. D2). New treatments may also need to consider changes in other modulatory neurotransmitter systems. The central role that dopamine plays in a range of behaviours and cognition creates difficulties in developing an effective dopaminergic drug to treat addiction that does not also produce serious adverse side effects.

### **Pharmacological Treatments to Reduce Reinforcement**

Another approach to treat addiction has been to block the acute dopaminergic response to addictive drugs by blocking dopamine receptors. It was hoped that DA antagonists would prevent the "high" of addictive drugs by dampening drug-induced DA increases in response to drug use, and therefore reduce their reinforcing effect. Several antipsychotic drugs, which are DA antagonists, have been tried, without success. While they were effective in reducing craving and the reinforcing effects of addictive drugs in a laboratory setting, this success did not translate into clinical trials. Antipsychotics are also not well tolerated by addicts who are particularly

sensitive to the extrapyramidal effects of D2 blockers, (e.g. disorders of movement and motor control such as those seen in Parkinson's disease) (Hyman, 2005).

The poor results of DA antagonists may be related to the fact that *some* people who are dependent on drugs such as alcohol and stimulants, have been found to have reduced D2 dopamine receptors in the NAcc,(Garavan et al., 2007; Cosgrove, 2010). It is uncertain whether this neuroadaptation is the result of constant increases in DA activity associated with chronic drug use, or due to a pre-existing vulnerability that predispose some people to drug use (Martinez et al., 2005). This reduction in DA activity is believed to be responsible for the anhedonia that many addicts experience once abstinent, and that can lead to relapse.

Given the role that dopamine plays in everyday motivation, blocking D2 receptors is also likely to decrease sensitivity to natural reinforcers. One drug that affects dopamine activity and has proven effective in the treatment of nicotine addiction is bupropion (Zyban) (Jorenby et al., 1999). Its exact mechanism of action is still uncertain although it appears to act by inhibiting the uptake of dopamine and noradrenaline (Ascher et al., 1995). Bupropion is also a nicotine receptor antagonist. Clinical trials are under way to investigate the use of bupropion in the treatment of methamphetamine addiction (Nutt and Lingford-Hughes, 2008).

DA partial agonists could theoretically reduce the symptoms of anhedonia that can trigger relapse, however, these drugs have not proven effective clinically. Aripiprazole, an antipsychotic used in the treatment of schizophrenia, and a D2 partial agonist (as well as a DA receptor antagonist), has not proven effective in addiction. Researchers are currently investigating a D1 partial agonist that also possess D3 antagonist activity (Iverson et al., 2007).

Disulfiram, an old drug that has been used in the treatment of alcohol consumption, may be showing promise in the treatment of addiction to psychostimulants. Disulfiram (or Antabuse) blocks the hepatic enzyme, ADH, which breaks down acetaldehyde, a by-product of alcohol that can cause aversive symptoms and discourage drinking. This has the same effect as the ALDH2 gene. Recent research shows that disulfiram also blocks dopamine beta-hydroxylase, a neural enzyme that converts dopamine to noradrenaline. Disulfiram can increase dopamine levels, as well as reduce noradrenaline, and may therefore be useful in the treatment of psychostimulant addiction (Preti, 2007).

### **Pharmacological Treatments to Reduce Cue-conditioned Craving**

As we discussed previously, events or stimuli associated with drug use can trigger intense cravings that lead to relapse. These cues become conditioned to trigger an expectation of drug reward that can lead to an aversive state if the expected drug reward does not occur. As we discussed in the previous section, research suggests that decreasing DA activity is responsible for cue-induced craving. Drugs which prevent this decrease were hoped to ameliorate craving.

It was thought that DA partial agonists would provide a small degree of reinforcement by slightly increasing DA activity, without providing too much of an addiction risk (remembering that any drug which increases release of DA in the NAcc has the potential to be abused). Such a treatment would theoretically be useful for treating other DA deficient consequences of drug abuse, such as withdrawal. It would also block the reinforcing effects of psychostimulant use, providing a welcome pharmacological option for psychostimulant abuse. Preclinical trials of the DA partial agonist (BP897) which demonstrated that it was effective in blocking cue-induced cocaine seeking behaviour, have not been repeated in a human population because of its toxicology in humans (Pilla et al., 1999). Drugs with similar pharmacokinetic properties are being investigated (Nutt and Lingford-Hughes, 2008). Preliminary studies of the dopamine receptor 1 (D1) agonists have been promising (Baler and Volkow, 2006), as has a partial agonist of the dopamine receptor 3 (D3) in treating cocaine dependence (Pilla et al., 1999; Lingford-Hughes and Nutt, 2003).

The use of substitutes (e.g. dexamphetamine, methylphenidate) to treat addiction to stimulants (by binding to DAT in order to increase dopamine activity) has been unsuccessful. The D2 selective agonists tested have also not proven effective. Pharmacological agents targeted at the other dopamine receptors appear more promising.

### ***Pharmacological Interventions in Systems Related to the Reward Pathway***

One could argue that an overemphasis on the role of DA in addiction has impeded the development of effective pharmacological treatments that do not act on this neurotransmitter system. The preclinical promise of dopaminergic drugs to treat addiction has not lived up to expectations. Clinical investigation of drugs that target other neurotransmitter systems that modulate the DA reward pathway may provide

greater success (Lingford-Hughes and Nutt, 2003). These related circuits indirectly affect the reward pathway by: regulating either dopamine cell firing or the release of dopamine in the NAcc (e.g. opioids, and the amino acids, glutamate and GABA); or they interfere with the postsynaptic response to dopamine stimulation (e.g. cannabinoids) (Iverson et al., 2007). Interventions in these processes provide some novel and promising treatments to emerge from neuroscience research. More empirical data is required on their safety and efficacy. Pharmacological interventions in each of these related systems are discussed below.

## **Opioids**

Recent research has suggested that changes in the opioid system play an important role in all forms of addiction, not just opioid addiction. There are three receptor subtypes that mediate the effects of endogenous opiates. Neuroimaging studies suggest that changes in mu opioid receptor levels may be fundamental in addiction (Zubieta et al., 2000). The kappa receptor may also play a role. Stimulation of kappa receptors reduces dopamine release in the NAcc that may be responsible for feelings of dysphoria. Delta antagonists reduce self-administration of alcohol in rats, and so may play an important role in reinforcement (Lingford-Hughes and Nutt, 2003).

Mu-opioid receptors (MOR) on GABAergic neurons in the VTA also play an important part in attenuating DA activity in the reward pathway. Studies have found that mu-opioid receptor levels are increased in recently abstinent human drug addicts (e.g. alcohol, cocaine and heroin) and these are correlated with craving (Zubieta et al., 1996; Heinz et al., 2005; Williams et al., 2007). Naltrexone has been shown to be effective in reducing the severity of lapses to alcohol drinking, presumably by reducing opioid mediated reward (Pettinati et al., 2006). Research has shown that the efficacy of naltrexone can depend on individual differences, such as the severity of dependence and variance in the MOR gene (Anton et al., 2006; Ray and Hutchison, 2007). The effects of opioid activity on GABA neurons is not the complete picture because naltrexone is not effective in nicotine or cocaine addiction (Vocci and Ling, 2005).

The mu-opioid antagonist, naltrexone, also reduces relapse in alcohol dependence (Volpicelli et al., 1995). The fact that naltrexone is effective in the treatment of addiction to substances other than opioids highlights the role that the opioid system plays in addiction. As discussed previously, naltrexone is a long-acting opioid receptor antagonist which blocks the effect of opiates like heroin. Naltrexone has

been shown to be effective in the treatment of alcohol dependence, probably because it blocks the actions of endogenous endorphins that are released by alcohol (Herz, 1997). Naltrexone has also been shown to be effective in the treatment of obesity (addiction to food) (Volkow and Wise, 2005) and gambling. It is one of a number of anti-craving drugs that have become a focus for research (O'Brien, 2005). Recent research suggests that a newer mu-opioid receptor antagonist which displays partial kappa receptor antagonism, nalmefene, may also reduce the consumption of alcohol (Srisurapanont and Jarusuraisin, 2005).

### **The Amino Acid Neurotransmitters: Glutamate and GABA**

Many of the neuroadaptations that are thought to occur in addiction involve changes in the prefrontal cortex that have numerous connections with the dopaminergic reward pathway. Activity in these cortical circuits is mediated by the amino acid neurotransmitters, glutamate and GABA. It is also likely that other yet to be identified neurotransmitters are involved. These neurochemicals accordingly represent promising targets for pharmacological intervention. Studies have begun to look at whether drugs that act on these systems reduce drug self administration in animals (Kalivas and Volkow, 2005). Treatments which affect the glutamate and GABA systems may also prove effective in the treatment of stimulant addiction. .

The amino acid, glutamate, is the principal excitatory neurotransmitter in the brain. The glutamatergic system is well placed to influence dopamine signalling because its neurons in the prefrontal cortex and amygdala make reciprocal connections with the dopaminergic mesolimbic reward pathway. The glutamate receptor subtype, N-methyl-D-aspartic acid (NMDA), appears to play an important role in addiction to nicotine, cannabis, alcohol and benzodiazepines (Wolf, 1998; Lingford-Hughes and Nutt, 2003). Antagonists of the NMDA receptor inhibit sensitisation to stimulants and the development of opioid dependence (Trujillo and Akil, 1995; Lingford-Hughes and Nutt, 2003). Co-treatment with the NMDA blocker, dizocilpine, also attenuates tolerance to opioids (Trujillo and Akil, 1991). There also appears to be a compensatory increase in the numbers of glutamate receptors in alcohol addiction that may explain the hyper-excitability seen in alcohol withdrawal. Acamprosate, a drug that is effective in treating alcohol withdrawal symptoms, decreases glutamate release (O'Brien, 2005). N-acetylcystein (NAC), an activator of the cystine-glutamate exchange, is currently in Phase 1 clinical trials for cocaine dependence (LaRowe et al., 2006). Not all NMDA receptor antagonists are clinically useful because some produce hallucinations and psychotic symptoms.

Dopaminergic activity in the reward system is under inhibitory control from GABA signalling, in particular the GABA-B receptor (Cousins et al., 2002). GABA agonists have been effective in reducing the reinforcing effects of a number of drugs, presumably by decreasing dopaminergic activity. For example, Baclofen, a muscle relaxant that stimulates the GABA-B receptor, has been shown to reduce the reinforcing effect of a number of addictive drugs, including heroin, psychostimulants and alcohol in animal studies. Preclinical studies in rats suggest that Baclofen may be an effective treatment of alcohol, cocaine and amphetamines (Cousins et al., 2002; Brebner et al., 2005). A recent clinical trial of Baclofen showed that it was also effective in reducing alcohol consumption in a population of alcoholic patients with severe liver cirrhosis (Addolorato et al., 2007).

GABA enhancing drugs maintain abstinence by preventing cue- and drug-induced increases in dopamine. There are several anticonvulsants or antiepileptics that have demonstrated promise in the treatment of addiction, although the mechanism is not fully understood. Valproate, tiagabine and topiramate have shown promise in treating alcohol, opioid and cocaine addiction (Kampman et al., 2004; Myrick and Anton, 2004; Zullino et al., 2005), while another antiepileptic, gamma-vinyl-GABA (vigabatrin) might also be effective (Brodie et al., 2005). Other antiepileptics have not had any effect, indicating that more research is required (Sofuoglu and Kosten, 2006; Johnson et al., 2007).

Glutamate is involved in the neuroadaptations that underpin the learning of addictive behaviours as a result of chronic drug use. Future research will investigate the possibility that glutamatergic drugs can be used to “unlearn” these behaviours by reversing the synaptic changes (Nutt and Lingford-Hughes, 2008). Glutamate, and to a lesser extent GABA, are also involved in the molecular processes, such as LTP and LTD, that are responsible for the synaptic changes that maintain addiction. Neuroscientists are currently investigating the signalling molecules within each neuron that produce the internal cellular processes that lead to synaptic plasticity, such as gene expression or gene upregulation, protein synthesis and protein trafficking (Calabresi et al., 2007). The molecules that sustain these processes may prove to be significant targets for the treatment of addiction, by helping to reverse or ameliorate the neuroadaptations associated with addiction (Calabresi et al., 2007). A great deal of research is required before this hope may be realised, but it holds

significant promise, particularly for addictions that do not yet have an effective pharmacological target.

### **Cannabinoids**

The cannabinoid receptor (CB1) system is believed to be involved in the neural processes underlying reward, learning and memory. This suggests that this system might also be a potential pharmacological target in the treatment of addiction. Drugs which act on the cannabinoid system have recently been shown to reduce the reinforcing effects of various drugs of abuse. The CB1 cannabinoid receptor modulates dopamine cells and postsynaptic responses from dopamine stimulation, and can therefore influence the reinforcing effects of drugs. The CB1 antagonist, Rimonabant, appears to attenuate the reinforcing effects of various drugs of abuse. Rimonabant was originally developed as a treatment for schizophrenia, based on the fact that cannabis can lead to psychosis. However, it was later found to be effective in the treatment of obesity and metabolic syndrome (Van Gaal et al., 2005). Preclinical studies also suggest that it may be effective in treating nicotine addiction (Le Foll and Goldberg, 2005; Le Foll et al., 2008) and in preventing relapse to the use of other drugs.

### **Corticotropin Releasing Factor and the Stress Response**

Chronic drug use also produces neuroadaptations in other neural systems that can significantly affect an individual's ability to refrain from using drugs (Baler and Volkow, 2006). There has consequently been an increased effort in recent years to develop pharmacological treatments that ameliorate these neuroadaptive changes. Changing the stress responses to chronic drug use is one important example.

Since stress is a potent trigger for relapse, dampening the stress response may be a way of reducing relapse to drug use (Bruijnzeel and Gold, 2005). The stress response is mediated by CRF in the HPA axis and amygdala. Drugs, such as CRF antagonists, which can interfere with the stress response may prevent relapse. Drugs which block CRF activity have been shown in animals to block the initiation of drug use and stress-induced reinstatement of drug seeking behaviour for a variety of drugs (Koob and Kreek, 2007; Koob and Le Moal, 2008). Dynorphin is another molecule in the stress pathway that is being targeted.

Oxytocin is a neuropeptide hormone that is involved in pregnancy and childbirth. However, more recently, its role in the formation of relationships (Pitman et al., 1993;



Insel, 2003; Heinrichs and Gaab, 2007) and the development of trust (Kosfeld et al., 2005; Domes et al., 2007b; Domes et al., 2007a) has been the focus of research. Recent research has suggested that it may be a possible target in the treatment of addiction (Kovacs et al., 1984; Sarnyai and Kovacs, 1994; Kovacs et al., 1998; Sarnyai, 1998). Oxytocin is released by the posterior pituitary and reduces stress, dampens HPA activity (Kovacs and Telegdy, 1988; Devries et al., 2007), and reduces dopamine transmission. Oxytocin also inhibits the development of tolerance to addictive drugs and reduces the symptoms of withdrawal from morphine in rats (Kovacs et al., 1984; Kovacs et al., 1998).

## **Memory Manipulators and Cognitive Enhancers**

Pharmacological treatments which either enhance or dampen memories associated with drug use have also been investigated as addiction treatments. The use of the adrenergic beta blocker, propranolol, interferes with the formation and recall of emotionally salient memories, and may be effective in the treatment of PTSD (Pitman et al., 2002). Propranolol may also prove to be effective in reducing conditioned responses to drugs such as cocaine (Kampman et al., 2001; Milekic et al., 2006). Memory enhancers have been suggested as an adjunct to psychotherapy because of the effectiveness of a similar approach in treating phobias.

Drugs which improve alertness and attention, such as modafinil which is used to treat narcolepsy, have been suggested as treatments for stimulant addiction. Modafinil appears promising in the treatment of cocaine addiction (Dackis et al., 2005).<sup>17</sup> The development of effective treatments for Parkinson's and Alzheimer's diseases which increase memory and attention, may also provide novel approaches to the treatment of stimulant addiction (e.g. ampakines).

## **Pharmacological Approaches to Minimising the Harmful Effects of Drug Use**

Research is underway to develop new forms of drugs which reduce the toxic or harmful effects of drug use (e.g. liver toxicity). Nutt (2006), for example, has suggested that neuroscientists should develop a less toxic, water soluble GABA-agonist that would produce the euphoric effects of alcohol without its untoward side-

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<sup>17</sup> Modafinil, while not addictive, has an abuse liability. It is already reportedly being abused by long-distance drivers to drive for longer and by athletes in competition. It is not yet clear what the harm of long-term modafinil use may be. There is also a question as to whether its (ab)use in examinations would be considered cheating.

effects (Nutt, 2006). An analogous approach has been suggested with tobacco harm-reduction in which cigarette smokers would be encouraged to switch from smoking to much less hazardous oral tobacco products, such as snus (Gartner et al., 2007). Snus has been treated to remove the primary carcinogens and because it is orally consumed, has a substantially reduced incidence of adverse health effects (e.g. lung cancer).

An alternative approach to harm reduction is using other drugs to mitigate the acute negative effects of particular drugs of abuse. One suggestion is to use drugs to prevent memory loss associated with alcohol intoxication (Nutt, 2006). A similar strategy is used in the prescription of combined pharmacological treatments of addiction with the aim of reducing the abuse potential of the treatment. One example is the combination of a small dose of an opioid antagonist, naloxone, with buprenorphine (marketed as Suboxone) to reduce injecting use of the diverted drug. Because of its low oral absorption (3 to 10 %) naloxone does not affect the reinforcing properties of buprenorphine when taken orally but precipitates withdrawal if the product is injected. It remains to be seen if this proves effective.

Another alternative is to develop drugs that reduce or prevent harms associated with chronic drug use. For example, drugs such as Acamprosate, which reduce glutamate activity, could be given to chronic drinkers to reduce the glutamatergic neural toxicity associated with withdrawal each morning. Researchers have also recently identified an antioxidant, Tempol, that can reduce oxidative neural damage associated with chronic cocaine use (Numa et al., 2008). As researchers identify the neuropharmacological basis for the harms of chronic drug use, we believe that there will be an increase in the use and demand for pharmacological harm-reduction treatments that are not substitution-based. A summary of all the main treatments for drug addiction in use or development are listed in Table 6.

## **The Pharmacogenetics of Addiction Treatment**

Pharmacogenetics has been suggested as one way to improve the modest success of addiction treatment. Genetic information (e.g. about drug metabolism or dopamine response to the drug) could be used to match addicts to the treatment most likely to enable them to quit. This approach has been most widely adopted to date in the field of nicotine dependence where genetic information is being used to decide whether a

smoker is more likely to quit with bupropion or NRT (Walton et al., 2001; Munafo et al., 2005; Lee and Tyndale, 2006).

A pharmacogenetic test for nicotine dependence, the Nicotest, has been marketed in the UK via direct to consumer advertising as a way of helping smokers to decide whether to use NRT or bupropion in a quit attempt. This involves assessing polymorphisms of the D2 allele and using this information to advise smokers to use bupropion or NRT. A number of clinical trials have been conducted to test the value of using this genetic information to tailor cessation treatment to smokers. Similar proposals have been made in matching treatments for other addictions to particular pharmacological treatments. For example, a recent study has found that naltrexone treatment of alcohol dependence appears to be more effective in individuals with a particular variant of the OPRM1 gene, the mu-opioid receptor (MOR) gene (Anton et al., 2008). Similar results have been seen in the treatment of opioid addiction (Lawford et al., 2000), as well as addiction to other drugs (Hejazi, 2007).

The two major issues in assessing addiction pharmacogenetics are: (1) will this approach be effective, that is, will the genotypes identified predict differential responses to treatment? And (2) if so, will the additional costs of genetic testing be justified by the improvements in outcome (Flowers and Veenstra, 2004)?

If we assume that the answer to the first question proves positive, how would we assess the cost-effectiveness of pharmacogenetics? We know that the cost-effectiveness of pharmacogenetic tests is affected by the characteristics of: the genes being tested, the condition being treated, and the treatments that genetic tests are being used to select among (Flowers and Veenstra, 2004).

<b>Proposed targets</b>	<b>Medication</b>	<b>Clinical effectiveness for</b>
<i>Interfere with the reinforcing effects of a drug:</i>		
<b>Substitution treatments</b>	Methadone	Opioids
	Buprenorphine	Opioids
	LAAM	Opioids
	Nicotine replacement	Nicotine
<b>Trigger aversion</b>	Disulfiram	Alcohol (cocaine) <sup>b</sup>
<b>↓ dopamine release</b>	Topiramate	Alcohol (cocaine)
(antiepileptics)	(Gabapentin)	(Cocaine)
	(Gamma-vinyl-GABA)	(Cocaine)
<b>Non-dopamine targets</b>		
mu-opiate receptors	Naltrexone	Alcohol and opioids
cannabinoid receptors	Rimonabant	(being tested for weight loss, nicotine and others)
GABA receptors	(Baclofen)	(Alcohol and cocaine)
<b>Interfere with drug delivery to the brain</b>	Vaccines	Nicotine and cocaine (heroin in development)
<b>Interfere with drug metabolism</b>	Methoxsalen	Nicotine
	Disulfiram	Alcohol
<i>Compensate for long-term effects of drugs:</i>		
<b>Interfere with conditioned responses</b>	Antiepileptics (above)	Alcohol (cocaine)
	Glutamate	
	Acamprosate <sup>c</sup>	Alcohol (cocaine)
	(Modafinil) <sup>c</sup>	
<b>Strengthen saliency of natural reinforcers</b>		
(i.e. Enhance DA function)	Bupropion	Nicotine
	(deprenyl + nicotine)	(Nicotine)
<b>Interfere with stress responses</b>	(CRF antagonist)	Not tested
<b>Interfere with withdrawal</b>	Clonidine	Heroin
	Benzodiazepines	Heroin
	Antiepileptics	Alcohol
	Propranolol	

<sup>a</sup> Medications for which there is only preliminary clinical data are identified in brackets to differentiate them from those for which there is proven efficacy.

<sup>b</sup> The effects in cocaine addiction are not understood but do not seem to be mediated by triggering aversive responses.

<sup>c</sup> Mechanisms of action are not properly understood.

TABLE 6. A SUMMARY OF CURRENT OR DEVELOPING TREATMENTS OF ADDICTION. (SOURCE: BALER AND VOLKOW (2006)).

Among the key characteristics of the gene being tested are its prevalence in the population of smokers and how well it predicts differential treatment response. Screening for rare polymorphisms is not very useful unless they are very strong predictors of treatment outcome, because a very large number of people will need to be tested to identify the small number of individuals who respond differentially to treatment. The predictive value of the polymorphisms for the outcome of interest (e.g. differential response to smoking cessation interventions) reflects the sensitivity and specificity of the genetic test for the polymorphisms and the penetrance of the gene, that is, the degree to which people with the polymorphism differ in their response to treatment from those who do not. A genetic test for a gene of low prevalence and penetrance is unlikely to be useful (Flowers and Veenstra, 2004). These are the characteristics of the alleles that have been evaluated to date in studies of nicotine pharmacogenetics (Lee and Tyndale, 2006).

We can specify the type of research required to assess the cost-effectiveness of addiction pharmacogenetics using Nicotest as an example. Nicotest uses the results of a genetic test for a polymorphism in the D2 allele to determine whether a smoker is more likely to quit smoking using NRT or bupropion (<http://www.nicotest.com/>). One could model the cost-effectiveness of Nicotest using empirical evidence on: the prevalence of the D2 polymorphism among smokers; its predictive value for success in quitting with NRT or bupropion; the cost charged for the test; epidemiological models of the tobacco-related mortality and morbidity that would occur among smokers who continue to smoke vs. those who successfully quit using these methods; and estimates of the costs of treating tobacco-related disease that have been averted by successful quitting.

The critical issue in evaluating the cost-effectiveness of Nicotest is the condition with which we compare its cost-effectiveness. A comparison condition is required to decide whether the improvement in cessation rate that is achieved by Nicotest is worth the additional costs incurred by the genetic testing and counselling that its use entails (Flowers and Veenstra, 2004; Munafo et al., 2005). This will require studies that compare the cost-effectiveness of Nicotest with simpler and cheaper methods of treatment selection, such as, avoiding matching by offering all patients the most effective treatment (averaged across genotypes) (Hall et al., 2002). The critical measure in this case will be the incremental cost-effectiveness ratio (ICER): the ratio of the difference in benefits between using Nicotest and not matching, divided by the difference in costs between these two approaches (Flowers and Veenstra, 2004).

In addition to cost effectiveness, evaluations of Nicotest will need to consider the social and psychological consequences of giving smokers information about their genetic susceptibility to nicotine dependence. The implicit assumption of pharmacogenetics is that this information will motivate smokers to use the treatment provided but this cannot be simply assumed to be true (Marteau and Weinman, 2006). We need to investigate the “folk genetics” of nicotine dependence: the everyday inferences that people in the community draw about the plasticity of smoking and its amenability to intervention if it is seen as being “genetic”. Specifically, we need to discover whether popular simplifications of smoking “genetics” entails a form of genetic reductionism (Nelkin and Lindee, 1995), namely, the belief that smoking is a fixed and immutable behaviour that can only be changed with great difficulty, if at all, by biological interventions (Nelkin, 1973). Two studies on smokers’ understanding of the implications of information about genetic risk for cessation suggest that smokers who accept the plausibility of a genetic contribution to cigarette smoking are less confident about their self-efficacy in quitting and more likely to see a biological intervention as required to become abstinent (Wright et al., 2003). More work is required on this issue.

## **Potential New Approaches to Drug Treatment**

Developments in medical technologies are opening up novel alternatives to pharmacological treatment of addiction. As they are novel they may have significant unintended consequences that need to be anticipated and evaluated. In addition, some of these technologies can be significantly invasive. However, they represent significant advances in the treatment of addiction, and increase the variety of approaches available to clinicians and addicted individuals.

### ***Immunotherapies***

Immunotherapies represent a new strategy in the development of addiction treatment. These are in the form of vaccines against the effects of nicotine, cocaine and heroin that act by binding to the target drug in the bloodstream and preventing it from reaching the brain. Drug vaccines are primarily intended to be used in relapse prevention but the term “vaccine” also raises expectations about their potential use to prevent drug addiction when used as a prophylactic treatment (e.g. in combination with genetic screening of adolescents for addiction susceptibility). The effectiveness

of such an approach is uncertain and even if successful, it would raise a number of ethical concerns that will be addressed below (see pp 121-124).

### ***Depot or Sustained Release Formulations***

Several research groups are developing implantable sustained release or long-acting formulations of effective drug treatments. So far, such developments have focussed on treatments that interfere with the pharmacological action of the drug of abuse (i.e. agonists, partial agonists and antagonists). Sustained release pharmacological treatments offer the significant advantage of overcoming the issue of poor compliance, that is, the difficulty in getting patients to continue to take the drug. Compliance is a persistent issue in many areas of medicine, but is particularly salient in psychiatry where an individual's condition may reduce their ability or willingness to comply, where patients may not wish to be treated, find the side-effects intolerable or undesirable, or do not believe that the treatment is required anymore.

The development of depot or sustained release treatments of addiction will make it possible to reduce dosing from a daily event to a monthly or even half yearly implantation, removing the significant burden of daily, or near daily dosing that is common to many pharmacological treatments of addiction. The inconvenience that this can cause should not be underestimated: daily dosing can have a significant impact upon work and family, and ultimately lead some to discontinue treatment, and eventually relapse. Implantable agonists or partial agonist treatments also reduce the risk of their diversion to black drug markets, as can happen where take away doses are given.

Currently, long-acting treatments of addiction are being investigated for opioid dependence, using the antagonist, naltrexone, and more recently the partial agonist, buprenorphine. Researchers in Western Australia have developed a naltrexone implant that is inserted subcutaneously for the treatment of heroin addiction. The implant is made from a patented polymer that contains naltrexone, which is released for several months (Hulse et al., 2004; Hulse et al., 2005b). Clinical trials show that the polymer implant itself (excluding the impact of the drug) is well tolerated, with infection occurring at the site of insertion in approximately 1% of patients (Hulse et al., 2005a). Studies by the Western Australian group have reported that the naltrexone implant reduces opioid-related deaths (Hulse et al., 2005a), decreases the incidence of BBV (Jeffrey et al., 2007), and has a positive impact upon work, family life, mental health and sleep (Ngo et al., 2007). Hulse et al. (2005b) have suggested

that these naltrexone implants can be used in pregnant women. This same group is also developing a slow release flumazenil (a potent benzodiazepine antagonist) implant for the treatment of benzodiazepine addiction (Nutt and Lingford-Hughes, 2008).

Naltrexone implants may pose risks that need to be considered when they are used in a population that often fails to adhere to treatment. While active naltrexone provides strong protection against overdose, failure to maintain adequate naltrexone levels can lead to overdose if they relapse to heroin use, using the same dose prior to detoxification (Hall et al., 1997). This was a significant problem with oral naltrexone, which required daily dosing. This problem led to the development of the long-acting implant. Research will need to consider the impact of removing the implant or failing to replace the implant within the required time on the risk of overdose and on the abuse of other drugs, such as alcohol, benzodiazepines, and psychostimulants. The studies so far have not examined these potential risks, and the implants have yet to undergo the necessary clinical trials required to be registered by the Therapeutic Goods Administration, as is required for all other pharmacological interventions. Their use has also been associated with a number of adverse events and deaths (Degenhardt et al., 2008; Lintzeris et al., 2008). These treatments have also been advocated for use under legal coercion (Caplan, 2006; Sullivan et al., 2008), a practice that raises a number of ethical concerns that are discussed below.

### ***Neurosurgery and Deep Brain Stimulation***

A radical, and so far rarely used treatment, is neurosurgical ablation of brain structures implicated in addiction. Neuroscientists in Russia and China have used neuroscience research on the effects of chronic drug use on the nucleus accumbens and the cingulate gyrus to justify the stereotactic ablation of these regions (Gao et al., 2003; Medvedev et al., 2003). Neurosurgery is the most invasive and permanent form of treatment used, and is often only considered appropriate in a few severe conditions where there are few options which have been tried unsuccessfully. It is generally considered a last resort in treatment, requiring careful consideration (Valenstein, 1973; Valenstein, 1986; Hall, 2006). The ethical implications of the social and political context in which these treatments have been used will be discussed in subsequent sections.



Deep brain stimulation (DBS) is another form of neurosurgery that has been suggested as a treatment of addiction (BBC News, 2007). It involves the insertion of electrical stimulating electrodes deep into the brain regions involved in addiction, such as the insula. When the electrodes are stimulated, activity in these areas can be manipulated. The use of DBS in these areas has so far only been trialled in obsessive compulsive disorder (Gabriels et al., 2003), although DBS has been used in the treatment of Parkinson's Disease and is currently being trialled in the treatment of depression. While this treatment is not as damaging as ablative neurosurgery, it does present considerable risks and can result in permanent damage. The side effects of this novel treatment are also unknown. Some patients with Parkinson's Disease who have been treated with DBS have developed impulsive behaviours that appear similar to addictive disorders (Frank et al., 2007). A patent has also been placed on the use of intracranial (vagal) nerve stimulation as a treatment for addiction.

### ***Transcranial Magnetic Stimulation***

Transcranial magnetic stimulation (TMS) is a far less invasive treatment that involves placing a small magnetic coil against an individual's skull in order to block or enhance neural activity in a particular cortical region (Machii et al., 2006). The coil produces a strong magnetic field that can change neuronal electrical activity (Pascual-Leone et al., 2002). By manipulating cortical activity, it is hoped that TMS might prove to be a useful treatment for a range of psychiatric disorders, including addiction (Ridding and Rothwell, 2007). TMS raises fewer health and safety concerns than neurosurgery or DBS because it does not involve physical penetration of neural tissue (Anand and Hotson, 2002). However, it has been reported to cause psychotic and epileptic symptoms in a minority of patients (Wassermann, 1998; Machii et al., 2006).

TMS is capable of producing significant behavioural changes. Studies have shown that a session of TMS can have a significant impact on the decisions individuals make (Fecteau et al., 2007), and may enhance cognition and memory (Illes et al., 2006a). A recent pilot study has shown that a session of high frequency repetitive stimulation of the right prefrontal cortex can reduce craving in cocaine addicted subjects (Camprodon et al., 2007). However, there are significant hurdles that will need to be overcome. Firstly, double blind studies using TMS are inherently difficult to conduct as it produces a contraction in the muscles of the scalp directly beneath where it is applied that is easily perceptible by subjects. Secondly, the effect size in

these experiments are very small, raising questions about its clinical usefulness. This technique therefore requires more research to evaluate its safety and efficacy.

### ***Applications of Neuroimaging and Neurocognitive Screening to Prevent and Treat Addiction***

Neuroimaging using fMRI, PET, single photon emission computed tomography (SPECT), magnetoencephalography (MEG), and electroencephalography (EEG) are non-invasive techniques that enable researchers to identify functional and structural abnormalities in the brains of addicted individuals. It has been suggested that these techniques might also be used in preventing addiction and developing more effective treatments (Volkow and Li, 2005b; Yucel and Lubman, 2007), but effectiveness (cost and otherwise) of such approaches has yet to be demonstrated.

#### **Prevention**

As with genetic screening, neuroimaging could be used to identify neuropsychological vulnerabilities that predispose some individuals to develop addiction if they use drugs (e.g. poorly functioning inhibitory control circuits). Neuroimaging studies have shown how some drug use produces cognitive changes that focus attention on drug use, and make strong urges to use drugs more difficult to resist. Neuroimaging has also helped to understand why adolescents are more vulnerable to drug use and more susceptible to its deleterious effects (Gogtay et al., 2004). Some have argued that neuroimaging may be able to help identify those who are more neuropsychologically vulnerable to the effects of drug use, particularly while young, or more likely to try them (Volkow and Li, 2005c), although this is an hypothesis that is yet to be borne out by research.

A significant problem with this idea is determining whether differences in brain structure and function are a result of chronic drug use, or precede drug use and possibly explain vulnerability to addiction. Untangling the origins of changes in brain function requires large prospective studies, that involve studying subjects from a young age, prior to drug exposure, and re-examining them over a period of years to see if there are differences between those who have and have not used drugs and become addicted. These are important studies, one of which is currently underway at Orygen, Australia.

Once these studies are complete, it is not certain that scientists will be able to identify neuropsychological changes that accurately identify those at risk, better than current

methods such as using family history of drug use, socio-economic status, and age of initiating drug use. Neuroimaging is also expensive. Given the current under-funding of addiction treatment, a higher priority might be given to education and other social initiatives to reduce drug use and addiction.

### **Treatment**

Neuroimaging has a greater potential role to play in the treatment of addiction. For example, neuroimaging may help to identify neuropsychological deficits that are the primary source of an individual's inability to stop using drugs (e.g. strong underlying urges for drugs, poor inability to resist impulses to use drugs, sensitivity to stress, or strong habit). This would allow clinicians to target specific pharmacological treatments to individuals that would increase their chances of success, assuming such treatments become available.

Researchers have been able to identify patterns of activation within the brains of addicted individuals during decision-making that predict whether that individual is likely to relapse to drug use (Paulus et al., 2005; Schutz, 2008). This may be significant in identifying which sort of psychotherapy an individual may find effective, as well as identifying those individuals who will require more intensive interventions (Yucel and Lubman, 2007).

Neuroimaging may also help clinicians to target more effective pharmacological treatments to individuals. The identification of specific neuropsychological deficits in an individual may allow clinicians to prescribe pharmacological treatments to ameliorate these deficits. For example, research has identified three triggers for relapse: cues associated with drug use (e.g. images of the addictive drug); stress; and drug priming (small amounts of a drug that lead to a relapse to a full blown binge). These triggers appear to be mediated by distinct neural pathways, although there is some degree of overlap. Preclinical studies have shown that some pharmacological medications are able to target each of these pathways, without affecting the other two (Shaham and Hope, 2005). By identifying patterns of neural activation in individuals, it may be possible to provide patients with pharmacological treatments that best remedy their particular deficit (Schutz, 2008).

If the cost of neuroimaging technology proves too large to justify its wide scale use in the treatment of addiction then neurocognitive tests, such as tests of attentional bias towards drug use, impulsivity, or the ability to resist immediate rewards, may be as

effective as imaging technologies in guiding treatment decisions, such as identifying those most likely to relapse. These tests are cheap to administer, and have been shown to be just as accurate in identifying those likely to relapse to drug use. They measure addicted individual's response time to certain tasks that reflect attentional bias towards drugs (Cox et al., 2002), or impairments in executive control (Goudriaan et al., 2008). Tasks measuring impairments in decision-making capacity (the Cambridge Gamble Task and the Iowa Gambling Task) in an opioid dependent population were also shown to significantly predict those who remained abstinent from opioids 3 months after treatment (Passeti et al., 2008). These tasks are extremely easy to administer, and may be of potential benefit in guiding treatment decisions, planning of treatment services and the allocation of resources.

Neuroimaging studies may also play an important role in developing better, more effective psychological treatments of addiction that target particular neurocognitive changes associated with addiction. The neuropsychological deficits discussed in the previous section, for example may be used to develop drugs that increase executive control, by increasing dopaminergic activity in the PFC, particularly during withdrawal and early abstinence when there is often a further drop in executive control; a time in which these resources are desperately required to resist increasing urges to use drugs.

Many psychotherapies aim to develop awareness of the costs and benefits of continued drug use thereby improving response selection (improving PFC function). Some also develop drug refusal skills and better ways of coping with craving by improving inhibitory control (improving aCG functioning) (Yucel and Lubman, 2007). Neuropsychological studies could strengthen the rationale for psychotherapies that aim to remedy deficits in decision-making and executive control or develop new skills. They will also help researchers and clinicians to understand the involvement of comorbid psychiatric conditions or behavioural problems that can interfere with treatment. They also provide a stronger justification for the need of public health funding of research and treatments which aim to ameliorate disruptions in psychological functioning.

## **Psychosocial Treatment of Addiction**

Psychosocial interventions such as, cognitive behavioural therapy, motivational interviewing, drug counselling, and 12-step support groups (based on the AA model)

provide an important adjunct to pharmacological and medical treatments in achieving a long-term successful outcome. While psychosocial treatments are outside the scope of this report, it is important to acknowledge the need for greater attention and investment in psychosocial treatment research. Advances in cognitive neuroscience showing cognitive deficits in impulse inhibition and a pathological focus on drug use in addiction highlight the importance of psychosocial therapies that can ameliorate these cognitive deficits (Volkow and Li, 2005b). Neuroscience may also help in designing therapies which are more effective for addicted individuals with particular kinds of cognitive deficits. The neuroscience of addiction vulnerability during adolescence may assist in driving social policies for dealing with addiction, such as prohibitions on alcohol and tobacco use in minors, and the importance of early education on the dangers of drug use.

## **Ethical and Policy Issues in the Application of Neurobiological Research on Addiction**

The evidence reviewed in earlier chapters suggests that many addictive phenomena have a genetic and neurobiological basis. The major practical promise of this work is to improve socio-legal responses to addiction, and specifically the treatment of persons with addictive disorders. Some leading addiction researchers, for example, argue that identifying the neural correlates of compulsive behaviour in addiction will lead to more options for the treatment of addiction, and to increased funding for addiction treatment (Dackis and O'Brien, 2005; Volkow and Li, 2005a). These are reasonable hopes, but they need to be tempered by pragmatic and realistic analyses of both potentially beneficial and unwelcome uses of neuroscience. In this respect, policy makers should be aware of the potential for the misrepresentation or misconception of neurobiological research, that may lead to community misunderstandings of the implications for addiction neuroscience; that is what it can and cannot achieve, and the how it should be best implemented. It is important that information presented is balanced so as to avoid any unintended backlash in the community or mistrust of neuroscience research of addiction. Failure to anticipate such misunderstandings may result in an unfavourable evaluation of the research, or biased and unethical uses of potential or emerging technologies for the treatment and possible prevention of addiction, as has occurred with other scientific advances (e.g. agrotechnology and genetically modified organisms (GMOs)). In this chapter we review some possible unwelcome uses of this research, with the aim of identifying ways of minimising the likelihood of their occurrence.

In order to realise the promise of addiction neurobiology, it will be necessary to address ethical doubts that this type of research raises about the capacity of addicted persons to provide free and informed consent to participate in studies that involve the administration of drugs of dependence, or to make choices not to use their drug of addiction. In this respect, we begin with a brief analysis of autonomy and addiction. We will then turn our attention to describing the ethical issues that researchers, clinicians and policy makers will also need to consider prior to the application of new treatments derived from addiction research so that they are translated quickly and economically into effective and appropriate treatments of addiction. The research and development of treatments of addiction requires significant investment with limited

funds, and it is critical that the financial support available is directed into areas that are most likely to deliver effective treatments of addiction.

Key themes that arise from this analysis are:

- More research is necessary to understand the effects of addictive drugs on the capacities of autonomy and self-determination. Two models predominate in current ethical discussions: the “disease” and the “sceptical” models of addiction; the application of these contrasting ideas will affect how people who use drugs are treated by society and the judicial system;
- The involvement of drug users in approved research should be reviewed for both clinical necessity and ethical justification;
- Societies should assess whether it is acceptable for the legal system to coerce addicted defendants to undergo drug and diagnostic tests and treatments, given the issues that this raises in respect to self-determination. A particular focus should be on ensuring the effectiveness, safety, and justification of using long acting treatments, such as depot medications and vaccines, under legal coercion.
- Advances in predictive genetic testing and neuroimaging that may enable society to identify “addicts” or predict individuals’ future risks of addiction will raise concerns about invasion of privacy and the use of such data by third parties (e.g. insurers, employers). Furthermore, society should consider the need for consumer protection against the over-interpretation of test results.

Society should be aware of the implications of developing drugs that modify neural pathways in novel ways. The use of pharmacological interventions to enhance or modify behaviour in healthy individuals risks medicalising behaviour via “diagnostic creep”, that is the encroachment of psychiatric diagnoses into the normal range of human behaviour. This may create new patterns of drug use, or lead to new forms of addictive behaviour (Brownsword, 2004; Hall, 2004).

The public and media interest in the results of addiction neuroscience research may lead to “hype and hope” in the addiction debate. Neuroscientists and geneticists have a moral obligation and professional interest in minimising popular misunderstandings of their work, particularly in the media, that may rebound to its detriment.

## Theories of Addiction: Sceptical Views and Medical Models

A key issue in debates about the ethical implications of addiction neuroscience is how much “autonomy” addicts possess, that is, how much capacity do they have to make free and informed “choices”. A detailed analysis of this issue is beyond the scope of this report; useful accounts can be found elsewhere (e.g. Levy (2006)). For our purposes, the important point is that different ideas about the autonomy of addicted persons may have different implications for the “ethical” use of new treatments arising from neuroscience research on addiction. For example, if addiction is seen as stripping addicts of all autonomy, the way is left open for paternalistic measures, that is, for making “decisions” *on behalf of* the addict in what we take to be the “best interests” of the individual.

On one hand, there are important questions about whose interests these interventions may serve. On the other hand, if drug users are considered to have autonomy, that is only temporarily or marginally diminished, it may still be possible to *involve* willing addicts in decisions about their own treatment; or at most to coerce them into making “constrained” choices, such as choosing between prison and treatment, if they have committed an offence to obtain drugs. In reality, the views taken on the decision-making capacities of addicts are likely to cover a spectrum of ideas. We favour the view that addiction causes a temporary loss of autonomy in certain circumstances (especially during intoxication or withdrawal) but most of the time, persons with addiction retains sufficient rational capacity to require their involvement in treatment decisions.

The options available for policies towards addiction therefore reflect judgements about what strategies are acceptable in preventing drug use and/or drug-related harm. The strategies used to achieve these aims need to balance what the state is justified in doing to individuals who sometimes act on temptation, impulse, compulsion or fail to act rationally (a so-called “paternalistic” approach), and other values such as individuals’ right to self-determination reflecting the “liberal” idea that individuals are the best judges of their own actions. In the following, we discuss how ideas about the autonomy of addicts may affect ethical judgments but we do not take a firm position on this issue. Nor do we recommend specific regulatory strategies. Before discussing these issues in more detail we outline two common ideas about



the nature of addiction and the decisional capacities of addicts that often implicitly inform social judgments and societal responses to drug use and addiction.

### ***The “Sceptical” Model***

The “sceptical” view of addiction is often seen as a continuation of the “common sense” position that “addicts” are simply drug users who knowingly and willingly choose to use drugs without regard for the consequences that their actions inevitably bring upon themselves and others. For those who espouse this view, it is commonsense that “addiction” has little or nothing to do with biological loss of autonomy (discussed below); “addiction” is a term used as an excuse for deviant behaviour. Such a view is *sceptical* of a biological approach to the treatment of “addiction”. Its proponents respond to addiction by primarily aiming to deter people from using drugs, and insist that users should take responsibility for the consequences of their actions (Szasz, 1975; Davies, 1997).

Sceptical views make sense of a number of features of “addictive behaviour”:

- Drug use is at least initially a voluntary choice that only leads to addictive patterns of drug use in a minority of those who use drugs;
- Among the minority of drug users who do become addicted, most stop using drugs by themselves (Peele, 2004);
- It is consistent with the everyday experiences of the majority of people who decide to stop using drugs and do so with a minimum of difficulty.

The prevalence of the sceptical view of addiction has led to the worldwide application of punitive laws to deal with drug users and deviant behaviour. These laws range from incarceration and forced or coerced “treatment”, to corporal and capital punishment for drug use. These approaches are justified by a “moral” rhetoric (such as the “war on drugs”) which suggests that deterrence, punishment and taking users off the streets is the best way to reduce drug use and associated crime. These policy responses are justified because, it is argued, drug users are fully capable of changing their behaviour when given the right inducements to do so. However, it has also been forcefully argued that the imprisonment is largely ineffective in reducing drug use and addiction. It also contributes to the social costs of addiction by imprisoning many drug users who typically return to drug use and re-offend on release from prison (Gerstein and Harwood, 1990; National Research Council, 2001; Marlowe, 2006).

## ***Neurobiological Theories of Addiction***

The fact that these policies have been so unsuccessful in reducing the drug use of addicted persons has prompted a search for alternative explanations that appeal to the effects that repeated drug use has on an individual's autonomy, and specifically on their ability to choose not to use a drug. In this respect, a number of dependable empirical observations are brought to bear on the "sceptics" view of drug use and addiction:

- A significant minority of people who use drugs become addicted to that drug, and the risk of becoming addicted depends on the way the drug is consumed and on its pharmacological action (Anthony and Helzer, 1991). Drugs that are injected or smoked, and which act quickly and for a short time (e.g. heroin, cocaine, and nicotine) are more likely to produce addiction than drugs that are consumed orally (like alcohol);
- There is also an identifiable subset of individuals who are more likely to develop an addiction. This includes people who have more contact with drugs or peers who use drugs, who use drugs at an earlier age, who are from socially disadvantaged backgrounds, perform poorly in school, have a family history of addictive behaviour, or suffer from a mental disorder (Hawkins et al., 1992).
- Evidence from twin and adoption studies also suggest that there is a substantial genetic contribution to addiction vulnerability (True et al., 1999; Ball and Collier, 2002; Hall, 2002b; Goldman et al., 2005). This has been estimated to be between 40 and 60% (Uhl et al., 2004). The continued use of drugs in the face of serious negative health and social consequences, and in the absence of any pleasure derived from consuming the drug all suggest that addictive patterns of drug use reflect more than mere wilful bad behaviour.

Some interpretations of neuroscience and genetic research in addiction has challenged traditional notions of addiction as a voluntary choice. These authors argue that the studies reviewed above suggest that prolonged drug use results in long-lasting, and possibly irreversible, changes in brain structure and function that undermine voluntary control (Leshner, 1997; Volkow and Li, 2004). As described previously, studies of the effects of repeated drug use on brain function, combined with knowledge of how environmental, genetic, and developmental factors can influence vulnerability to addiction, increase our ability to treat and possibly prevent

addictive disorders (National Academy of Sciences, 1996; Leshner, 1997; Cami and Farre, 2003). Thus, these authors argue, neuroscience evidence should prompt societies to change the way in which they think about addiction, and the social policies that they adopt to deal with it (Leshner, 1997; Volkow and Li, 2004; Dackis and O'Brien, 2005). While punitive sanctions may deter non-users from using drugs, one of the key outcomes of this model of addiction is that we need to provide more effective medical treatments of addiction and invest in neuroscientific research that will provide these new treatments rather than simply imprison those with drug dependence.

Neurobiological theories of addiction attempt to identify the molecular and cellular mechanisms of how drugs act on the brain in ways that may impair control over drug use. Such a theory of addiction now in the ascendant in the United States is the "chronic, relapsing brain disease model" (Leshner, 1997). According to the National Institute on Drug Abuse (NIDA), addiction is caused by chronic self-administration of drugs that produce enduring changes in brain neurotransmitter systems that leave addicts vulnerable to relapse after abstinence has been achieved (Leshner, 1997; Volkow and Li, 2005c). In the same way that cardiovascular disease is a result of damaged or dysfunctional heart tissue, the chronic disease model of addiction holds that addiction is the result of disordered neural tissue (Volkow and Li, 2004). In the follow discussion, we will refer to the two models of addiction as the "sceptical" and "disease" models, although it should be noted that these contrasting views lie along a continuum rather than comprising discrete categories of views.

### ***Policy Implications of Neuroscience Addiction Research***

The assumption often made by addiction neuroscientists is that increased knowledge of the effects of drug on the brain will lead to a better understanding of addiction and acceptance of the idea that addiction is symptomatic of neurological dysfunction. It is also claimed that acceptance of these views this will lead to more effective pharmacological strategies to treat and even prevent addiction. Many also hope that their work will reduce community scepticism about the "reality" of addiction and eventually supplant the "commonsense" view (Leshner, 1997; Volkow and Li, 2004; Dackis and O'Brien, 2005). The policy focus will then switch from a disproportionate emphasis on punitive policies, to policies that aim to reduce stigmatisation and break the addiction cycle.

Those who are more sceptical of the “disease” model of addiction point to a number of potentially less welcome consequences. Some argue that the “disease” model undermines any justification for harsh punitive measures towards drug use. Others more favourable to the view of addiction as a chronic brain disease, may be concerned this view is seen as warranting heroic and risky interventions in the brain function of addicted individuals, such as ultra-rapid opiate detoxification for heroin dependence (Hall, 2000), or the neurosurgical treatment of addiction (Hall, 2006).

Although the debate has been simplified here, recent ethical debates about addiction have focused on the question of how much autonomy addicted drug users have. This debate is complex and beyond the scope of this report, but ideas about the autonomy of addicts is related to the “sceptical” and disease models outlined above that inform societal responses to addiction. The “disease model” of addiction tends to focus on “medical” responses to the treatment and prevention of addiction. It also suggests that addiction impairs autonomy and so might be used to justify coerced treatment if addicts are seen to be at the mercy of the state of their neurotransmitters (Valenstein, 1998) and hence require the state to act “for the good of the patient” (Caplan, 2006). By contrast, the “sceptical” model tends to deny any lack of control on the part of addicts, and favours more punitive responses to drug use.

Another risk is that the “disease” model of addiction may lead to an underestimation of the value of social policies in reducing drug use and drug-related harm. By focusing on addiction as a brain disease, one runs the risk of ignoring the detrimental effects of drug intoxication in person who do not have an addiction. For example, a policy focus on alcohol dependence overlooks the very serious health risks (such as accidents and violence) caused by alcohol intoxication (Hall and Sannibale, 1996). Some argue that it could lead addicts to abdicate any responsibility for their behaviour (Nelkin and Lindee, 1996; Valenstein, 1998; Dalrymple, 2006).

Deterministic accounts of addiction are not confined to neurobiological theories of addiction. Similarly deterministic arguments have been made for the role of social factors that lead to drug use and addiction in vulnerable individuals, such as socio-economic background, or early adolescent exposure to parental addiction. However, neurobiological accounts arguably make the scientific case for a causal account more compelling and persuasive than appealing to social circumstances: the brain seems much closer to controlling behaviour than historical events in a person’s childhood. Appeals to “faulty genes” also provide a more mechanistic account of

addiction that may make urges to use drugs seem more difficult to resist. The likelihood is that the majority of those “addicted” will have vulnerabilities that are both neurobiological and sociological in origin. As our knowledge develops, however, it will be necessary to provide accounts that provide a balance between the two extreme views. It is also very likely that the nature of the balance between these two categories of factors is different for every individual. For these reasons, we do not take any position on these issues in the following discussion. Rather, we simply elucidate the relevant issues that may affect how neuroscience research affects the way in which we treat persons with addiction.

### ***Implications for Human Neuroscience Research on Addiction***

If taken very literally, the “brain disease model” of addiction may undermine the capacity of neuroscientists to undertake research on the effects of drugs of addiction, drug analogues, or drug-related cues (e.g. injecting equipment) on the behaviour of addicted individuals (Hall et al., 2004b). The international ethical consensus is that biomedical research on humans (Brody, 1998; Jonsen, 1998) requires independent ethical review of the risks and benefits of proposed research, free and informed consent from research participants, and protection of privacy and confidentiality of the information that is collected (Brody, 1998). Research involving persons who are cognitively or physically impaired requires special ethical consideration (Brody, 1998) because such vulnerable persons may not be capable of providing informed consent (National Bioethics Advisory Commission, 1999).

The commonly held view among addiction researchers has been that drug dependent people are able to give free and informed consent so long as they are not intoxicated or suffering acute withdrawal symptoms (Adler, 1995; Gorelick et al., 1999). However, this assumption has recently been challenged by some ethicists who argue that the behavioural characteristics that define addiction, namely the “compulsion” to use drugs and the “loss of control” over drug use, prevents those who are drug dependent from giving *free* and informed consent to participate in research studies that involve the administration of their drug of dependence (Charland, 2002; Cohen, 2002). These arguments could be seen to be given more weight by recent imaging studies of addicted brains which suggest an impaired ability to make decisions (Volkow and Li, 2004). There are good reasons to doubt the scientific basis of these arguments (Carter and Hall, 2008b). However, if ethics review committees were to accept them, then no experimental or clinical research

could be undertaken in which drug dependent people receive their drug of dependence or an analogue.

Neuroscientists need to be aware that these arguments are being made, largely based on over-interpretations of neuroscientific evidence, when communicating the results of their research. While it is doubtful that addiction produces the kind of impairment necessary to make the significant assertion that drug dependent individuals completely lack the autonomous decision-making capacity to refuse drugs, there are clearly circumstances, such as acute withdrawal and intoxication, where autonomy is impaired to varying degrees (Walker, 2008). There are few studies investigating under what conditions and in what contexts the ability to refuse drugs is impaired in addicted individuals, and more research is urgently required (Carter and Hall, 2008a).

### ***Use of Coerced Treatment of Addiction and Judicial Policy***

The most obvious potential benefit of neuroscience and genetic research on addiction is improved treatment of drug dependent persons. However, studies suggesting that addiction is a disease that impairs decision-making and undermines the capacity to consent to treatment may be used to justify the increased use of legally coerced treatment. Appeals to diminished autonomy are often used to justify treatment strategies that override or ignore the views of addicts in their own “best interests”, rhetorically appealing to the need to “save addicts from themselves”. There are a number of ways in which individuals may be coerced into treatment, that differ in the degree in which they override an individual’s own choices (see Pritchard et al. (2007) for a comprehensive review). Coerced treatment is most often advocated for drug dependent people who have committed a criminal offence, referred to as *legally coerced treatment*. We describe the use and justification for legally coerced treatment below:

- 1) Legally coerced drug treatment for persons charged with, or convicted of, an offence to which their drug dependence has contributed, is usually provided as an alternative to incarceration under the threat of imprisonment if the person fails to comply with treatment (Hall, 1997; Spooner et al., 2001). The person is clearly given limited options; and thus is considered to have a basic capacity to make some choices. One of the major justifications for this practice is that treating offenders’ drug dependence will reduce the likelihood of their re-offending (Gerstein and

Harwood, 1990; Inciardi and McBride, 1991). This is not an argument in the person's "best interests", because they are considered able to make their own choices. "Best interests" arguments involve decisions that are made on behalf of a patient. Legally coerced treatment via the criminal justice system appears to justify paternalistic measures in order to protect others and deter further illegal activity. Thus, while arguments can be made for this practice it should not be confused with the idea of acting in an addict's "best interest"

2) Legal sanctions should be in line with a consensus view on drug treatment under coercion prepared for the World Health Organization (WHO) (Porter et al., 1986). This view concluded that such treatment was legally and ethically justified only if (1) the rights of the individual are protected by "due process" (in accordance with human rights principles);<sup>18</sup> and (2) effective and humane treatment is provided.<sup>19</sup> Some argue that any form of treatment is ineffective if compulsory, suggesting that rehabilitation requires internal motivation (Newman, 1974). If treatment under coercion were ineffective (as Newman claims), then there would be no ethical justification for providing it. In the absence of due process, coerced treatment would become *de facto* imprisonment without judicial oversight.

3) The uncertain benefits of coerced treatment have led some proponents to argue that offenders should be allowed two "constrained choices" (Fox, 1992); although there is considerable debate as to whether these are "real" choices. The first choice would be whether they participate in drug treatment or not. If they declined to be treated, they would be dealt with by the criminal justice system in the same way as anyone charged with their offence. The second constrained choice would be given to those who agreed to participate in drug treatment: this would be a choice of the type of treatment they received. This is a significant issue in the treatment of addiction, as the types of treatment provided can be motivated by punitive rather than medical responses, leading to the use of less effective treatment options. Clearly, programs which aim to increase participant involvement and choice in treatment offer a more ethically acceptable form of coerced treatment. Studies have also shown that coerced treatment programs that require some "voluntary interest" by the offender

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<sup>18</sup> A human rights approach may be characterised as defining both an agent's *capacity* for autonomy *and* the moral value arising from political and material conditions which make it possible for individuals to *exercise* their autonomy.

<sup>19</sup> The concept of "humane" is understood to be context based, because although coerced treatment may appear to be "inhumane" in one jurisdiction, it may be considered as closer to "humane" in another country where stiffer penalties, such as the death penalty, are used.

are also more effective than coerced treatments that do not (Gerstein and Harwood, 1990).

4) If pharmacological treatments are used under legal coercion, their safety, effectiveness and cost-effectiveness should be rigorously evaluated (National Research Council, 2001). Prescribing drugs that interfere with brain circuits responsible for addictive behaviours may have effects on other aspects of their lives, such as their ability to make decisions (Bechara, 2005), derive pleasure, and form and maintain social bonds (Aragona et al., 2006). These drugs may even diminish an individual's free will or autonomy, even if taken with consent (Caron et al., 2005).

We generally avoid "rights" terminology in the following discussion, not least because "rights" are complex and controversial concepts. Nonetheless, societies need to ensure that due process is observed in providing legally coerced addiction treatment. In light of the potential new treatments discussed below, it is important that new treatments and interventions for addiction have been proven to be effective and safe, and that they are used in a way that is *proportionate* to other state-sanctioned punitive measures.

## **Practical Applications of Genetic and Neuroscience Research**

The ethical and social issues raised by neuroscience and genetic research on addiction (Hall et al., 2003; Hall et al., 2004b; Ashcroft et al., 2007) can be considered under two broad headings: (1) ethical issues that arise from the potential use of technologies developed from neuroscience and genetic research, and (2) the broader social and ethical implications of the impact of addiction neuroscience research on public understanding of, and policies towards, addiction. In the following sections we outline the ethical and social issues that will require more systematic and detailed analysis by neuroscience researchers, ethicists, policy makers and the broader community. Our focus is inevitably on some of the more speculative future uses of improved understandings of addiction neurobiology to prevent addiction. This reflects in large part the media's fascination with possibilities that may seem unlikely to occur (e.g. universal vaccination of adolescents against addictive drugs). These scenarios do nonetheless need to be considered because media discussions of these possibilities may affect public attitudes towards addiction neuroscience.



Addiction neurobiologists will need to be able to explain the implausibility of some of these potential applications of their research.

### ***Predictive Genetic Testing***

If susceptibility genes are identified for addiction risk then children and adolescents could be genetically tested and those at higher risk offered preventive interventions to reduce their likelihood of using drugs (Collins, 1999). The potential benefits of such a test would be informing individuals about their susceptibility to addiction, potentially increasing their ability or motivation to refuse drugs, and thus allowing them to make better choices by, for example, avoiding circumstances in which they may be offered drugs. A more advanced response, assuming that effective preventative technologies and behavioural interventions are developed, would be to identify individuals with genetic predispositions and to offer such assistance. It is also possible, although perhaps unlikely, that preventative measures would be imposed upon “high risk” individuals. The result of such testing may be that one might see fewer individuals “risking” the criminal justice system, because they chose, or were compelled, to avoid the effects of addictive drugs. A second possibility is that individuals thought to be “at risk” may be helped or even coerced into social programmes (for example new housing or education schemes) that keep them away from drugs and environmental situations that may lead them to use drugs.

There are a number of reasons why, on current information, the use of predictive genetic testing, and especially genetic screening for addiction, is unlikely to be an effective policy (Holtzman and Marteau, 2000; Hall, 2005).

(1) Multiple genes predispose to a common disease; therefore individual susceptibility alleles only predict a very modestly *increased risk* of dependence (Hall et al., 2004a). Testing multiple genetic variants that were individually weak predictors would improve prediction (Khoury et al., 2004) but the larger the number of genes that are involved in disease susceptibility, the less useful *most* individuals will find information about their genotype (Hall et al., 2004a; Khoury et al., 2004). This is because as the number of alleles increases, the risk distribution tends to the log normal (Pharoah et al., 2002), meaning that the number of individuals with a very high risk combination of multiple genes is small and the majority of individuals are at an average genetic risk. This will also require a very large number of individuals to be

screened to identify the few who have a significant risk (Vineis et al., 2001; Yang et al., 2003).

(2) Predictive genetic testing may have unintended adverse effects. This would be the case, for example, if testing individuals for susceptibility to addiction *increased* their preparedness to try drugs, or reduced their willingness or belief in their ability to refuse drugs. This may be a problem, for example, if individuals were prompted to test the accuracy of genetic predictions (Hall et al., 2002). It would also be of concern if a particular genetic make-up led individuals to believe they were able to use drugs without risking addiction. Under these circumstances, a negative genetic test result could encourage drug use, risking the acute harmful effects of drug use and intoxication, while a positive result may encourage fatalistic attitudes to drug use, that is, the belief that an individual is unable to prevent or overcome addiction regardless of their choices.

There has been little empirical investigation of how genetic information may be acted upon by dependent or vulnerable individuals. While it is reasonable to think that genetic knowledge enables an individual to be prepared or take precautionary action, it would be mistaken to assume that this information will not have any negative consequences given the stigma involved in addiction.

(3) Some argue that screening is only ethically justifiable if there is an effective intervention to prevent the disorder in those who are identified as being at increased risk (Khoury et al., 2003). In the absence of such interventions knowledge of increased risk may lead to discrimination or stigmatisation without providing any benefit to the individual being tested. However, others argue that it may allow individuals to better plan their future or to make more informed decisions about their lives.<sup>20</sup> One such option that this opens up is a “choice” to avoid taking a drug if one is at risk; although this simplifies the possible circumstances and context of decision-making (Carter and Hall, 2008a; Walker, 2008). No interventions currently exist to prevent addiction, although the prospect of preventive vaccination against drugs such as cocaine, opiates and nicotine, or long-acting antagonists may raise this possibility in the future (Hall and Carter, 2004).

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<sup>20</sup> This argument has been used in the testing for Huntington’s chorea, although the situation is different because individuals not only plan their future, but avoid the inheritance of the disease to children (who can be screened). Thus “treatment” may be considered as avoidance of the inheritance of the disease.

## ***Vaccines to Treat and Prevent Addiction***

Researchers are now developing immunotherapies (e.g. vaccines) that treat drug addiction by blocking the psychoactive effects of a drug by either stimulating the immune system to produce antibodies (active immunisation) or through the introduction of synthetic monoclonal antibodies into the blood stream (passive immunisation) (Harwood and Myers, 2004). These antibodies bind to the target drug, preventing it from acting on receptors in the brain (Vocci and Chiang, 2001; Nutt and Lingford-Hughes, 2004).

Studies have shown that drug vaccines reduce the rush and euphoria associated with the target drug, the amount of drug that reaches the brain, dopamine release in the nucleus accumbens, the rate of clearance across the blood-brain barrier, and the volume of drug distribution, and self administration of the target drug (Hall, 2002a; Kosten and Owens, 2005). Vaccines have a very clear advantage over traditional small molecule pharmacological approaches (e.g. agonists and antagonists) in that they are long-lasting, highly specific, and as they remain primarily in the blood stream, have no apparent central nervous system side effects. These advantages suggest that immunotherapies may be effective in reducing relapse to drug use, a major hurdle in overcoming addiction.

There are a number of ethical issues that ought to be considered before the deployment of vaccination program to treat or prevent addiction. These issues make it unlikely that preventive vaccination programmes will provide an effective method of preventing illegal drug use and addiction.

(1) There are questions regarding the extent to which individuals would have to give consent. For example, it is likely that immunotherapies would be most often used in situations that are inherently coercive, e.g. when treatment is the result of encounters with the justice system. If such individual can give consent (i.e. the “sceptical” model is used), then vaccinations may be “offered” (or coerced), for example, as a condition of release from prison or to avoid incarceration. Addicted persons could even be compelled to do so in order to protect the interests of the foetus in pregnancy (from the direct effects of the substance use). They could also be used to “control” parents involved in the child welfare system in order to protect the interest of children from deviant parenting behaviour.

The ethical hurdle is that such treatments transgress traditional bounds of autonomy. Without a “best interest” defence, such measures would have to overcome this hurdle by appealing, for example, to problematic ideas of protecting the “interests” of the public. The problem is that it is sometimes difficult to disentangle the effects of drugs from drug-related behaviour (caused by other social, environmental and psychological determinants), and therefore the focus on addiction may become disproportionate.

Given that adolescent drug use is a strong risk factor in developing addiction, it is perhaps not surprising that it has been suggested that some parents may want to “vaccinate” their children (Cohen, 1997). As minors, children would not be legally able to consent to vaccination, but some have argued that vaccination against nicotine and other drugs is another decision that parents should be able to make on *behalf of their children* (Cohen, 1997). Given that there is a fundamental difference in vaccinations to prevent infection and vaccines to control behaviour, coerced or compelled measures are likely to be contested by those who place a high value on personal autonomy (Hasman and Holm, 2004).

(2) If the “disease” model is used, then individuals may be “treated” in their “best interests” without requiring consent. This approach may be used by the treating physician to “repair” or “reinstall” autonomy. This is not necessarily contentious, and is an established practice in medical settings. However, if autonomy is only impaired *temporarily*, an issue may arise in the use of vaccines in emergency situations that leads to lasting effects of the “vaccination” after autonomy is re-established, such as continued non-consensual “medication” and the consequences of the detectable presence of the vaccine (see (4), below).

The lasting effects of drug vaccines may be an issue for anyone who does not directly “choose” to use them. This is a special concern in the vaccination of minors. The way in which such vaccines are used therefore will come down to decisions about the capacities of young people or drug users (whether they are “addicted”, autonomous, or incapacitated), and the benefits that may accrue to society from vaccination. For example, should paternalistic measures be welcomed in the interests of protecting others? What are the effects of such interventions on other important principles such as privacy and liberty (Ashcroft et al., 2007)? One concern is if a diminished respect for autonomy is encouraged by the political, legal and social systems, then this may lead to the erosion of an individual’s interests in the interests

of society. Conversely, it is possible to argue that addicts give up certain interests when they start to use illegal substances, and in this case the state's interests may overrule those of the addict.

(3) Vaccines may also prove counterproductive if an individual attempts to overcome the antagonistic action of the vaccine by increasing the drug dose. Those who ambivalently agree to vaccination may later switch to using other possibly more dangerous drugs, different routes of administration (e.g. intravenous injection), or much higher than usual doses (Murray, 2004). Vaccines may also paradoxically make experimentation with drugs seem less risky, and therefore unwittingly increase drug use. The likelihood of this occurring should not be underestimated given the compulsion and motivation to use drugs, even in the face of certain negative consequences. The use of vaccines under any form of coercion will require careful monitoring by treating physicians and this may be an added economic burden on the health system.

(4) Vaccines will produce long-lasting (possibly life-long) markers that will be detectable in the blood and urine, and may lead to false positive drug tests (Murray, 2004). This raises the issue of confidentiality and discrimination which could discourage some from seeking immunotherapy. It is another risk that must be weighed when considering the ethical acceptability of using vaccines under coercion, or without freely given consent.

(5) Vaccines do not ameliorate underlying problems that may be associated with compulsive drug use and addiction (such as craving, helplessness, diminished executive control and withdrawal that may lead to relapse), or comorbid mental disorders (Ashcroft et al., 2007). Thus, while vaccines may well find a place in the treatment of addiction, they should not necessarily be seen as "magic bullets". Vaccines, like traditional addiction medications, will presumably need to be used in conjunction with behavioural treatments if life-long abstinence is to be achieved (Nutt and Lingford-Hughes, 2004).

(6) The use of a vaccine may also block the action of agonists or partial agonists (e.g. methadone and buprenorphine for opioid dependence) eliminating the future use of maintenance therapies. This would be disastrous if an effective and inexpensive treatment was developed which was blocked by vaccines. Vaccines

may also block the action of medications used in the treatment of other physiological conditions (e.g. opioid analgesics for pain relief) (Ashcroft et al., 2007).

There are also major practical obstacles to the preventive vaccination of children. First, the limited period of protection provided by existing vaccines would require booster injections, perhaps every two or three months throughout adolescence (Kosten et al., 2002). Apart from the time and organisation that such programmes would involve, some have argued that such exposure to needles and desensitisation will compound the “drugs problem” in adolescents, and may contribute to this population's distrust of adults or rebellion against the system. Second, the fact that the vaccine could be circumvented by using higher doses of drugs means that vaccination could be counterproductive if adolescents were prompted to test its efficacy. Furthermore, experimentation would not itself be deterred, and overdose – albeit at higher thresholds – would still be a risk. Third, it would be costly to universally vaccinate children with a vaccine of modest preventive efficacy (Hall, 2002a).

Vaccination of “high risk” adolescents seems a more plausible and less expensive option. But the feasibility of even this approach is doubtful given the low predictive validity of genetic screening (outlined above), the doubtful preventive efficacy of drug vaccines (Cornuz et al., 2008), and the possible adverse effects of vaccination (in addition to those mentioned above). The latter include stigmatisation of those who screened positive, and continued or even intensified discrimination of that group by other communities, or against them by third parties, such as life or health insurance companies (Hall, 2005).

### ***Relapse Prevention and Maintenance with Depot Medications***

Depot medications are sustained-release formulations of current medications for treating addiction, most often antagonists that block the brain receptors for the target drugs. They involve a slow, timed release of medications to counteract the effects of drugs. Depot medications have an advantage over traditional oral treatment medications because they only need to be taken once a month (or even less often), compared to 3 to 4 times a week for the conventional medical treatments. This has made depot medications an attractive option in preventing relapse. Sustained-release preparations of the antagonists naltrexone for alcohol and opioid dependence (Kranzler et al., 1998; Comer et al., 2002) and lofexidine for nicotine

dependence (Rawson et al., 2000) have been developed. A slow-release buprenorphine formulation is also being developed for the treatment of opioid dependence (Sobel et al., 2004).

The ethical considerations for the use of sustained release antagonists are similar to those for immunotherapy (Murray, 2004). As with immunotherapies, the use of depot medications for preventing relapse is most likely to occur in situations where capacity to give consent is compromised – either through the “addiction” itself or the constrained options “offered” to the drug user. The advantage of depot medications to vaccinations is that the treatment will not be detectable once the depot medication is used up, posing less of a concern for privacy and discrimination. However, depot antagonists also present similar safety concerns regarding changes in patterns of drug use or attempts to overcome their antagonist effects (Murray, 2004). It is also possible for treated individuals to remove some formulations of depot medications which will need to be considered, particularly in the coerced use of depot naltrexone, where failure to comply with treatment can lead to overdose death should the individual return to opioid use, as most do.

### ***Diagnostic and Predictive Uses of Neuroimaging***

Neuroimaging may prove a useful clinical tool in the diagnosis and treatment of addiction by identifying individuals with different subtypes of addiction or comorbid mental health issues, or particular cognitive deficits that require specific types of treatment. Neuroimaging, in the future, could perhaps play a role in ensuring that consent to treatment or research is valid by confirming that an individual possess the necessary decision-making capacity.

The ability to identify the neural correlates of addiction may also have other uses outside the clinic. For example, neuroimaging studies are able to detect dramatic changes in limbic responses to drug-related cues that would identify an individual as drug dependent (Childress et al., 1999). This may be of interest to third parties (e.g. employers). Advances in neuroimaging technology may also make it possible to obtain personal information about an individual that may predict their behaviour or identify aspects of their personality (Fischer et al., 1997; Fischer et al., 2001; Canli and Amin, 2002; Farah and Wolpe, 2004; Singer et al., 2004; Abler et al., 2005). Neuroscience investigations may also provide information that predicts disease risk in the same way as genes diseases like Huntington’s disease (Greely, 2002; Foster

et al., 2003). Characteristic patterns of brain activity in childhood and adolescence, for example, may predict increased risks of addiction later in adult life (Volkow et al., 2003).

These possibilities raise two ethical issues:

(1) Future improvements in neuroimaging may, even if imperfectly, disclose facts about a person that they may prefer to keep private (Ross, 2003). Furthermore, there are risks that such information will be used in discriminatory ways (Canli and Amin, 2002; Farah and Wolpe, 2004; Illes et al., 2004a; Anon, 2005; Illes and Racine, 2005; Illes et al., 2006). The use of neuroimaging technologies raises the same ethical issues (e.g. privacy and discrimination) that are raised by testing for alleles that predict an increased risk of serious neurological disease (Greely, 2002). This issue is amplified if imaging is conducted under coercion. Furthermore, because the changes in the limbic regions that respond to drug-related cues persist well into abstinence, there is the possibility that an individual recovering from addiction will be discriminated against despite being drug-free.

(2) There are also concerns with respect to consent, given that these neuroimaging tests could be applied using images of drug cues presented without the subject's awareness (Whalen et al., 1998).<sup>21</sup> Given the enormous costs associated with addiction, this technology may be used by employers, insurance companies, and courts. Important ethical issues would be raised if persons are compelled to undergo these tests by courts, insurance companies or employers. During the course of neuroimaging studies, up to 40% of brain scans of research participants show "suspicious" brain anomalies, with between 0.5 to 8% of research brain scans uncovering clinically significant neuropathology (Illes et al., 2004b; Illes et al., 2006).

### ***Neuroenhancement***

Most psychotropic drugs are first developed for therapeutic purposes such as to repair cognitive deficits, or to improve mood or attention or modify stress responses. Drugs developed for these purposes to treat addiction and other mental disorders are increasingly being used for non-medical reasons, such as to improve scores on exams, to enhance sociability or other desirable social traits, or to cope with highly competitive or stressful environments (Farah et al., 2004; Volkow and Li, 2005c;

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<sup>21</sup>It is possible to mask images by presenting them for intervals that are too short to be perceived consciously so that the viewer is not aware of having viewed the image, yet produces changes in neural activity that are detectable by neuroimaging.



Chatterjee, 2006). The enhancing effects of these drugs are often discovered serendipitously by persons using them for medical reasons (Ragan, 2007).

The ethical debate over the use of drugs for enhancement purposes involves arguments about the distinction between “enhancement” and therapy that are beyond the scope of this report (see Academy of Medical Sciences (2008)). Suffice it to say, there is a fuzzy line between technologies which raise the baseline of human capacities in impaired persons and other medical and social interventions, such as viral vaccines and education, which also contribute to “enhanced” human state.

The interest in enhancements in drug addiction is mentioned in this report because there is an apparent growing trend in the use of drugs to enhance performance in “normal” well-being (Parens, 1998a; Parens, 1998b; Parens, 2002); or to make one feel “better than well” (Elliott, 2003; Caplan and Elliott, 2004; Hall, 2004). Arguably, addiction can be seen as a failed attempt to enhance mood and attention. Such use may lead to addiction to new drugs, should they be habit forming, or to new patterns of drug abuse that may become chronic and produce significant harm (e.g. the use of stimulant drugs that people may feel socially compelled to use in order to meet some social demand, such as work deadlines). As we described previously, drugs that are developed to treat addiction act upon cognitive pathways, such as learning and memory, stress, anxiety, motivation and reward. The introduction of these technologies into medicine needs to consider the potential for such use in order to minimise the harm caused and prevent any unnecessary backlash that may hinder the valid therapeutic use of these medications in the treatment of addiction.

Some critics have suggested that well-known psychiatric medications, such as the selective serotonin reuptake inhibitors (SSRIs, e.g. Prozac), methylphenidate (Ritalin), and modafinil, are already being used by those who are not suffering from a mental illness in order change mood and personality or improve cognition and attention (Fukuyama, 2002). There is already speculation that drugs being developed to treat Alzheimer’s disease and post-traumatic stress disorder (PTSD) will be used by healthy individuals to enhance memory and cognition (Hall, 2003; Glannon, 2006; Chatterjee, 2007). There is anecdotal evidence of individuals using Prozac and other SSRIs with the aim of reducing the neurotoxic effects of MDMA or the “come down” (the negative after effects of an MDMA high). Most abused drugs began life as a medical intervention. In light of the history of drug use, these examples would indicate that the enhancement use of novel drugs is highly likely.

1) There are reasons to be concerned about the possible harms that individuals who use enhancements might experience. Adverse side effects to therapeutic drugs are common but these risks are generally outweighed by the relief from the symptoms of disease and disability they offer. However the balance between adverse effects and uncertain benefits of enhancement is less clear in healthy individuals (Wolpe, 2002; Chatterjee, 2004). The situation is analogous to the use of steroids to heal injuries and to enhance performance in sport.

2) Several drugs, including modafinil, SSRIs and beta-adrenergic antagonists have been used in the treatment of addiction (Lingford-Hughes and Nutt, 2003; Dackis and O'Brien, 2005; Dackis et al., 2005; Volkow and Li, 2005c). While this would not preclude their use, the possible consequences of this – including the short- and long-term effects – will need to be considered before addiction treatments gain market approval. There may be other “corrective” uses of such substances, for example at the organisation level to improve conduct (for example, behavioural enhancements) or productivity (such as reduced susceptibility to events which may limit performance and to improve performance), including prisons and workplaces (Academy of Medical Sciences, 2008). The potential for non-medical use of pharmacological technologies raises a number of challenges that society will need to deal with. For example, if an effective drug emerged that increased performance for those working in performance intensive professions, such as pilots or surgeons and even truck drivers, would we allow, and even more strongly, encourage its use if it was shown to increase safety. The advent of cognitive enhancing drugs will force society to reflect on what is acceptable drug use, when should such use be prohibited and when can such prohibitions be enforced.

3) The widespread use of enhancement technologies also has broader social implications. Some have argued that pharmacological enhancement may exacerbate existing social inequities (Fukuyama, 2002; Parens, 2002; Farah et al., 2004) while others see this as more a criticism of existing social hierarchies than a compelling objection to enhancement (Caplan, 2002). Private education and healthcare, academic coaching and cosmetic surgery are all forms of “enhancement” that are tolerated or encouraged in society, but which give people an “unfair” advantage. Some have argued that this objection could be overcome with respect to pharmacological substances by making all forms of enhancement freely available to all at low cost, e.g. publicly subsidising the use of enhancement technologies (Caplan

and Elliott, 2004), although the economic viability of this a suggestion is yet to be established. Where enhancements are used in competitive situations, and they are unsafe, there are strong arguments against their use (this is a common argument found in sports doping). However, such objections are less convincing when drugs are used in “non-competitive” situations, such as enhancing everyday memory to improve wellbeing. Policy makers face the same problem in that the line between competitive and non-competitive use is not clear. The use of cognitive enhancers in exam preparation and performance by university students, has now occurred over 6 decades (Rasmussen, 2008).

Widespread use of enhancement technologies may also raise standards for what is considered “normal” (Farah et al., 2004; Farah, 2005; Parens, 2005). Critics suggest that this form of social coercion would lead to a spiralling of pharmacological use as individuals endeavour to keep up with society (Chatterjee, 2006). This might be thought of as “indirect” coercion, where there is pressure on individuals to take drugs to stay on an equal footing with other users. This enhancement dilemma may also be felt acutely by parents in deciding whether to give their child “every opportunity”. Such a trend could increase discrimination against the disabled and those with medical conditions who decline to be enhanced (Parens, 2002). However, proponents of enhancement question whether those who do not want to be enhanced should be able to coercively prevent those who do from being enhanced (Caplan, 2002; Caplan and Elliott, 2004).

## **Future directions for addiction policy**

### ***Neuroscience and the Media***

Public interest in scientific findings and the political imperative for scientists to justify public funding have increased pressure on scientists to report their research findings in the popular media (Resnik, 1998). Given public interest in neuroscience research, and the potential for misunderstandings to rebound to the detriment of the research, neuroscientists and geneticists arguably have a moral responsibility to be proactive in their dealings with the media (Blakemore, 2002). They specifically need to ensure that accurate information is released to the media and that their publications include prominent disclaimers that correct predictable misinterpretations of their findings.

Furthermore, the media has an important role in educating the public about drug use, treatments and interventions. There are at least three issues to raise here:

(1) Scientists and researchers need to make it clear that addiction is not a simple single-gene disorder, that is, it is not the case that if you have “the gene” then you will become addicted and that you won’t if you don’t. It is important to understand the limitation of deterministic ideas of genetics, and how misunderstanding may effect “at risk” individuals or how they may be treated by others in the community.

(2) Given the seductive power of colourful brain images, neuroscientists also should clearly convey the limitations of neuroimaging as an experimental and diagnostic tool (Dumit, 2004). They need to caution against assuming that the results of imaging studies on selected severely addicted patient populations can be extended to all addicted individuals. The claims of entrepreneurs promoting these technologies to the public (e.g. truth-telling, personality matching, and as tests of marital fidelity) raise the need for consumer protection against the over-interpretation of equivocal test results and bogus claims (Caplan, 2002; Farah, 2002; Farah, 2005).

(3) Research is required to find out what members of the public believe about drug use and possible interventions and treatments. The Academy of Medical Sciences in the UK conducted an insightful consultation in this respect. For example, the public was critical of the media coverage of celebrity drug users, which portrays them as glamorous and far removed from the “reality of cocaine addiction” (Academy of Medical Sciences, 2008, p. 110). In this regard, more research is required to identify public attitudes towards new technologies

4) Research is also required to identify the best and most effective way of transmitting information from the research laboratory to the public.

### ***The Tasks Ahead for Ethics***

A major challenge for addiction policy and ethics will be finding ways to acknowledge the neurobiological contribution to drug use and addiction while recognizing that both are nonetheless affected by individual and social choices. In the best of all possible worlds, addiction neurobiology may allow us to reconsider our social responses to the minority of drug users who become addicted by reducing their stigmatisation and increasing their access to more effective psychological and biological treatments.

However, an improved understanding of the neurobiology of addiction will not relieve society of the obligation to try to prevent problem drug use that does not involve addiction, by reducing susceptibility to its appeal and addressing the social conditions that contribute to personal vulnerability (Spooner and Hall, 2002).

## **Audit of Australian Addiction Neuroscience Research**

Currently, little is known about the depth and variety of neurobiological research on addiction in Australia. We consequently do not know how it compares with, or differs from, international neuroscience addiction research, where Australia's research effort in this field has been focussed, and where research is lacking. The purpose of this audit was to summarise the type of neurobiological research on addiction that is being undertaken in leading Australian research centres, such as: the Orygen Centre and the Department of Psychiatry, University of Melbourne; Department of Pharmacology, University of Adelaide; the Neuropathology Laboratory, The University of Sydney; and the Addiction Research Centre, Howard Florey Institute.

Informed public debate is required if Australia is to derive the maximum benefit for public health and public good, at minimal social cost, from the substantial investment in genetic and neuroscience research in Australia (Independent Working Group on Brain and Mind Disorders, 2003). This audit and summary of current addiction neuroscience research in Australia will form the basis for analyses of existing strengths and reserve research capacity that could be engaged if more funding were to become available. It also enables an anticipatory analysis of some of the ethical and policy implications of potential applications of addiction neuroscience to the treatment and prevention of addiction disorders. This will allow us to identify and propose solutions to address the social, legal and technical issues that may be raised in applying results of neuroscience and genetic research on addictive disorders to improve public health and the public good.

### ***Significance of Audit***

The audit and analysis of current addiction neuroscience research in Australia will help to:

1. Provide an improved understanding of addiction neuroscience research in Australia.
2. Compare the state of Australian addiction neuroscience research with that conducted internationally.
3. Identify Australia's research strengths and highlight areas where more research and investment is required or lacking.

4. Identify any research areas of addiction policy issues unique to Australia (e.g. indigenous drug use and public health policy).
5. Provide a resource to allow researchers to collaborate more easily.
6. Identify priorities for research and development to ensure that technologies based on genetic and neuroscience knowledge are implemented in a way that maximises their benefits and minimises any adverse effects on public health.
7. Provide considered, evidence-based information for the development of public policy relating to the management and social implications of developments in genetic and neuroscience research on the addictions.

### ***Aims of Audit***

The 4 major aims of the audit of Australian addiction neuroscience are to produce:

1. A detailed directory of neurobiological addiction researchers and research groups within Australia, that includes:
  - names and locations of neurobiological addiction researchers in Australia
  - profiles of the major addiction research groups in Australia, including their major research focus and experimental approaches to studying addiction, a list of peer-reviewed publications, and hyperlinks to addiction research centre websites, and researcher profiles.
2. A comprehensive, searchable bibliographic database of addiction neuroscience publications from Australia researchers in the last 10 years.
3. A quantitative analysis of Australian addiction neuroscience research, including:
  - Type of research (e.g. animal studies, cognitive neuroscience, psychiatric genetics) conducted in Australia
  - Profile of Australian research groups
  - Types of drugs being studied
  - Comparison to international research
  - Impact of Australian research
4. A qualitative summary of addiction neuroscience research in Australia

## 1. Identifying Australian Addiction Neurobiologists

The methods used to identify and characterise neurobiological addiction researchers and groups in Australia involved a series of web-based searches, email interviews, “snowballing”, and searches of relevant publication databases (e.g. PubMed, BIOSIS Previews). These are detailed below:

1. Email interviews of members of the steering committee and project team to identify an initial list of high profile researchers and research centres.
2. Web-based searches to develop a state-by-state directory of Australian addiction researchers and research groups:
  - a. Expert and staff directory searches of Australian university websites, using the terms: addiction, drug abuse, and substance abuse
  - b. Conference website searches to identify those presenting neurobiological research of addiction, including: Australian Neuroscience Society Conference 2006-2008, Australian Professional Society on Drugs and Alcohol (APSAD); International Brain Research Organisation Conference 2007 (Melbourne), International Society for Biomedical Research on Alcoholism (ISBRA) World Congress 2006 (Sydney), Addiction Neuroscience Network Australia (ANNA) workshop 2006 (Hamilton Is)
  - c. Addiction Neuroscience Network Australia website
  - d. Search of the Australian National Council on Drugs’ (ANCD) *RADAR* website to identify past and present research projects on addiction neuroscience and genetics, using the search terms: brain, neuro\*, genetic\* (where \* is a wildcard)
3. Email interviews of researchers identified previously to:
  - a. Collate recent publications (up to the last 10 years)
  - b. Characterise research focus
  - c. Identify current projects or in press publications not indexed in literature databases, or on university websites.
4. Search of relevant citation databases, including PubMed (Medline/National Library of Medicine) and BIOSIS Previews:
  - a. Using author name search for researchers listed in directory
  - b. Search by Australian affiliation to pick up articles by researchers not identified by web-based search.



From our searches and email responses (method outlined above), we identified 61 Australian researchers working in addiction neuroscience and genetics, and provided a description of the type of research that they have carried out. These details have been collated in a directory, with links to research group websites, researcher profiles, and email addresses (see file “*Australian Research Directory*” attached). This search confirmed our initial impression that although there are very few specialised addiction research centres in this field in Australia, a large number of researchers do some work within addiction neurobiology, and they primarily work in small groups within University biomedical, psychology and psychiatry schools.

From the research profiles and publications provided by the each of the researchers, as well as the profiles found on university websites, each of the research groups were allocated into one of 4 research categories (see below for a discussion of how these categories were identified and characterised) that we think best reflects the type of research being conducted at the group. The categorisation of these research groups, and the primary researchers, are listed in Appendix 1.

## **2. Creation of the Publication Database**

The publication database was compiled using the Endnote software (Thompson Scientific, Endnote v10.). Publication records were retrieved from the two major indexing databases in the biological and chemical sciences (BIOSIS Previews: <http://www.biosis.org/> also from Thompson Scientific) and biomedicine (PubMed: <http://www.ncbi.nlm.nih.gov/sites/entrez>). These databases were chosen for their depth of coverage, and because they each apply a highly consistent system for categorising research publications according to a number of keywords or subject heading terms, that will be used to refine and analyse the publication database.

It was anticipated that the searches would retrieve a large number of irrelevant articles as typically happens in publication searches. Irrelevant publications may be unintentionally retrieved for several reasons, including:

- Other authors with the same name as the target author
- Publications by the target author in another research field
- Publications by the target author that fall outside our remit (e.g. non-neuroscience, non-addiction). The latter is common in addiction research which is often multidisciplinary, where researchers may work on several different aspects

of addiction, or where a particular research group uses a neuroscientific technique (e.g. neuroimaging) to study a range of different psychiatric disorders (e.g. schizophrenia, obsessive compulsive disorder (OCD), depression, and anxiety disorders).

All of the researchers identified in (1) were also asked, via email, to supply a list of addiction-related publications. Publication lists obtained from respondents have a number of limitations: they are limited to those researchers who are able to respond, and author reports of their own publications often contain errors as reporting on publications is a time consuming task that can easily lead to misreporting or failure to include all papers.

Publication databases offer a number of advantages for citation retrieval. They enable the collection of useful citation information, such as article abstract, keyword and subject headings (important for keyword searching of publication lists), number of citations (an indicator of the impact of the research), web link to a full article pdf, and author affiliation. This information is important in refining, analysing and quantifying the publication data. The publication lists obtained from respondents enable us to validate the publication search process and to verify that we have retrieved all relevant publications.

### ***PubMed and BIOSIS Previews Searches***

Searches of these databases were performed using the names (last name and first initial) of the 61 researchers previously identified. We initially searched the BIOSIS Previews database as this was deemed to apply a more systematic keyword or subject heading system that would provide more power during the refinement and interrogation of the final publication database. As BIOSIS Previews is a database aimed at the biological and chemical sciences, we anticipated that it may not index some of the target articles in the cognitive and behavioural sciences. A comparison of the collected records with the publication lists provided by the researchers confirmed this. A search of PubMed retrieved all other relevant articles.

Searches of publication databases retrieve records for a number of types of publications (e.g. meeting abstracts, conference papers, letter etc) in addition to peer reviewed journal articles that are not normally collected in publication analyses. We decided to include the following letters, commentaries and reviews, in addition to

peer reviewed journal articles, as they reflect the particular views of Australian researchers and their engagement with the international scientific community. We however, excluded meeting abstracts as these are often developed into peer-review articles, and may misrepresent the quantity of research being performed at a given centre.

### ***Refinement of the Publication Database***

The results of these searches were imported into the reference software, *Endnote 10* and used to create a master publication record database. There were 2,057 records in this initial database. A large number of these articles (1,615) were either not relevant (e.g. not by correct author), or outside the remit of the audit (i.e. comprising research that was neither neuroscience nor addiction). A number of searches and limitations of the database were employed to remove these unwanted records. In order to be included, publications needed to meet the following criteria:

1. Addiction neuroscience research
2. Australian research
3. Target author

#### **1. Addiction neuroscience research**

Many of the researchers identified also published research in other psychiatric fields, in addition to addiction. This was for a number of understandable reasons. First, many of these studies used the same tools and methods they had applied to addiction (e.g. neuroimaging, neuropsychological testing) to study other psychiatric disorders (e.g. schizophrenia). Second, there is also a large degree of comorbidity between other psychiatric disorders and substance abuse. Third, different psychiatric disorders also involve many of the same neurotransmitters, neural regions and cognitive processes. Therefore a search strategy had to be devised to limit the database to articles relevant to the study of addiction.

One difficulty was distinguishing between studies on the neuroscience of addiction per se and more basic neuroscience research on the genetic, pharmacological, neurological and cognitive processes that overlap with those involved in addiction. The latter type of studies may use drugs of addiction as tools to understand brain function. Such studies typically only investigate the acute effects of addictive drugs, and do not investigate their effects on behaviours that are typical of addiction. While this is important research which can have a significant impact on our understanding

of addiction, inclusion at this stage would interfere with our analysis of research specifically looking at addiction in Australia. Many of these studies were excluded by narrowing the database, although the publication records for this research have been retained in a master searchable publication database. We have focussed this part of the audit on research which specifically studies neurobiological and cognitive changes associated with addiction, and addictive behaviours; that is the effects of addictive drugs:

- chronically, over long periods of time
- that produced tolerance and withdrawal
- on difficulties in stopping drug use, abstinence, craving and relapse
- that led to psychological and/or physical harm (e.g. psychotic episode, overdose).

This approach did not include studies which looked only at the pharmacological properties of addictive drugs that are unrelated to addictive use (e.g. metabolism of ethanol by the dehydrogenase enzymes; half-life of different methadone isomers; impact of cannabinoids on gastrointestinal function).

The following search strategy was used to limit the publication database to addiction research. We included articles *containing* any of the terms:

- “addict” OR “dependence” OR “abuse” OR “misuse” OR “alcohol” OR “tolerance” OR “withdrawal” OR “overdose” OR “abstinence” OR “self-administration” OR “behavioural sensitisation” OR “behavioral sensitization” OR “conditioned place preference” in *any field*

Note that we used the term *contains* in Endnote’s search function. For example, the term “addict” retrieves articles that contain the words “addict”, “addicts”, “addiction”; and the term “alcohol” will return articles containing the terms “alcohol”, “alcoholism” and “alcoholic”. Searching within *any fields* ensures that all articles published within an addiction or drug abuse journal, or written by researchers at addiction research groups, are retrieved. The articles excluded by this search strategy were checked to ensure that no relevant articles were omitted: 722 publication records were identified by this search strategy and placed in a separate Endnote library. These records were then manually sorted to ensure that only the relevant articles remained, and manually

cross-checked against the publication lists provided by the researchers to ensure that no articles were missing.

## **2. Australian Research**

Australian researchers living in Australia at the time of audit were our primary focus. We have however also included some research by scientists working in Australia currently, but who were not living in Australia at the time that the work was done. The main reason for doing this was to make a clear distinction that would simplify the database searches. It also had the advantage of allowing us to identify the research experience and knowledge that is being brought to the country that may affect the type and quality of the future work. This is consistent with other common publication analysis methods.

In the process of identifying addiction researchers to be included in the audit (part (1) above), we restricted ourselves to those researchers that met our definition of “Australian” described above. A database search using these names (once any non-target authors of the same name have been eliminated) was restricted to Australian researchers so defined.

## **3. Target Author**

We had to ensure that all articles retrieved were by the target author, and not someone else with the same last name and first initial. As there are no authors of the same name working within the addiction field in Australia, a search limited to addiction research will exclude any non-target authors.

## **3. Quantitative Analysis of Publication Database**

### ***Neuroscientific Approaches to Investigating Addiction***

The neuroscientific study of addiction encompasses a spectrum of scientific approaches to investigating its subject. Defined broadly, neuroscience covers nearly all levels of understanding: physical chemistry of protein folding and binding; the inorganic chemistry of ion flows that sustain neuronal signalling; genetic and molecular activities that underpin cellular behaviour, and allow neural cells to communicate with each other and form complex neural circuits; the anatomy of neural circuits that produces complex behaviours, thoughts and emotions; and the

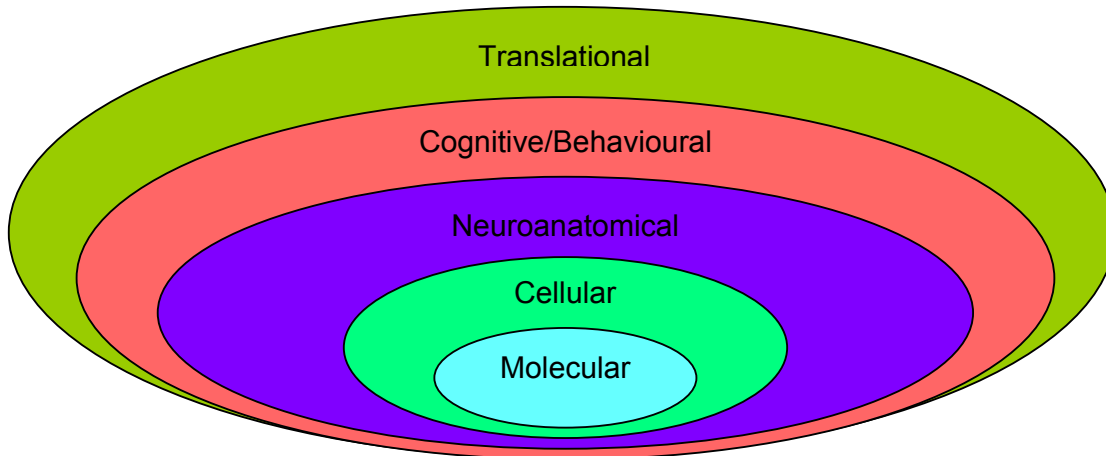
study of the cognition and behaviour of individuals affected by addiction. Neuroscience can also include computational mathematics that enables researchers to develop computer models that mimic aspects of human cognition and neuronal behaviour. However, such a broad view was too encompassing for our purposes and would include so many areas of research that it would make our analysis of addiction neuroscience research in Australia difficult to interpret. A narrower, more specific definition of neuroscience was required.

In the view of many neuroscientists, neuroscience refers narrowly to the physicochemical study of cellular and molecular interactions that underpin behaviour. While these processes are a central part of neuroscience research, to exclude psychological and cognitive study of addiction would be to take an *a priori* position on the nature and origin of addiction. An overly reductive view of brain and mind would also ignore the important progress being made by neurocognitive researchers in understanding addiction, and the role of psychological and behavioural therapies in the treatment of addiction.

Neuroscience is more generally understood as the study of the brain and behaviour. Popular notions of neuroscience research include studies of neurochemical imbalances, abnormal electrical activity in particular regions of the brain, or genetic predispositions to develop psychiatric disorders or display specific behaviour. Neuroscience also includes the study of molecular and cellular processes, such as cellular proliferation, differentiation and migration within the brain, neurochemical processes such as intracellular signalling, synaptic plasticity and cellular modification. For the purpose of this report, we will also include studies of the genetic bases of behaviour (including addiction) within the rubric of neuroscience or neurobiology. This reflects the view that genetic influences on neuropsychiatric conditions are ultimately expressed neurochemically within the brain (see Gallinat et al. (2008) and Caspi and Moffitt (2006)). In this report, neuroscience refers to the study of the molecular (including genetic), cellular, neuropsychological and cognitive or behavioural processes that underpin addiction, as depicted in Figure 11.

As the figure suggests, the different levels of neuroscientific investigation are not discrete. Levels of neuroscientific investigation are not simply hierarchical, but are embedded, and in practice, are rarely studied in isolation. This is particularly true of the study of addiction which is a quintessentially complex behavioural disorder that

cuts across most of these levels of observation. It therefore requires the use of a variety of neuroscientific approaches and techniques to fully understand it.



*molecular* - genes, neurotransmitters, intracellular signalling molecules, transporters

*cellular* - molecular trafficking, synaptic signalling, proliferation and differentiation

*neuroanatomical* - neural circuitry, functional organisation

*cognitive/behavioural* - learning, memory, executive control, emotion, motivation

*translational* – efficacy and safety, public health policy, ethics, education, resource allocation

FIGURE 11. LEVELS OF NEUROBIOLOGICAL STUDY OF ADDICTION

The neuroscientific study of addiction includes, but is not limited to, the following types of research: animal models of drug self-administration; electrophysiological study of neuronal firing in live animals and tissue culture; the study of genetic, pharmacological and neurological changes on animal behaviour; human neuropsychological testing and neuroimaging studies of drug effects and the effects of chronic drug use on the brains of persons with an addiction; psychopharmacological and molecular genetic studies in humans and animals; genetic epidemiological studies of drug use and addiction; and clinical trials of new drug or medical treatments for addiction suggested by the findings of addiction neuroscience. These approaches are complementary, and the integration of their findings promises to provide a more complete, although complex, understanding of addiction and addictive behaviour.

Ideally all addiction neuroscience research would be conducted in functioning human subjects. There are, however, physical, economic and ethical constraints that make some types of research in humans impermissible or undesirable (e.g. administering drugs with the aim of producing or inducing addiction to study its correlates in brain function). Consequently, a great deal of research on the effects of chronic drug administration on brain function is conducted in animals (e.g. mice, rats and monkeys) or on human tissue (e.g. autopsies, analysis of blood samples).

There are limits to what animal studies can tell us about addiction in humans. Fortunately, the advent of non-invasive neuroimaging techniques has enabled scientists to begin to study the impact of drugs and drug addiction on living, cognitively competent, human subjects. This has been an important advance in our understanding of the neurobiology of addiction because it has enabled the findings of research on the effects of chronic drug administration in animals to be validated in humans. In this section we describe the classification of addiction neuroscience research that we have used to characterise such research being conducted in Australia.

### ***A Classification of Addiction Neuroscience Research***

As the preceding discussion indicates, it is difficult to precisely define the limits of neuroscience research. Most observers would agree that research that involves molecular and cellular studies of the brain is the central object for neuroscientific inquiry. It becomes less certain where the limits of neuroscience exist as one moves



away from this central foundation: as we move further away from these core ideas, the defining boundary becomes fuzzier. Most would include studies of changes in the brain function of human subjects, pharmacological or neurophysiological, associated with particular behaviours or cognitions. However, considering any study of behaviour casts the net too wide to include most research in the older traditions of psychology and sociology.

We needed to develop a characterisation of neuroscience that was broad enough not to presuppose the results of the research (as discussed previously), but not so broad as to include psychology, psychiatry and sociology as mere subdisciplines of neuroscience. For the purpose of this report, we have categorised research in addiction neuroscience into four categories. Firstly, we have differentiated between animal and human research based on the qualifications made above. Second, we have subdivided human research into 3 additional categories. Each category of addiction neuroscience research relies on tools of investigation (e.g. animals, tissue or human subjects) and experimental techniques (e.g. genetic screening, neural activity or cognitive capacity) This classification has been derived in part from a review of the research literature and in part from the profiling of research in Australian addiction neuroscience research centres described above. The latter information included the discipline in which the research group was located; the descriptions of the work conducted within each research group as listed on their website; and researchers' own descriptions of their research. These categories of addiction neuroscience research are:

1. Animal studies of addiction

- Pharmacology of acute drug effects
- Molecular genetics of acute and chronic drug administration
- Models of human addictive behaviour (e.g. chronic self-administration of drugs, learned place preference, behavioural sensitisation, and relapse)
- Neuronal electrical activity in addiction or in response to addictive drugs
- Functional neuroanatomy of the effects of chronic drug administration

2. Human neuropathological studies

- Pharmacology and post mortem neuroanatomical studies of the effects of chronic drug use
- Genetic influences on neuropathology

### 3. Cognitive Neuroscience (or Neuropsychology)

- Imaging of neurochemical responses to acute and chronic drug use in human subjects
- Imaging of neuroanatomical changes in human chronic drug users
- Neurocognitive changes in response to acute and chronic drug use in human subjects
- Genetic and environmental influences on neuropsychological test performance
- Human clinical studies of addicted persons that *measure neurophysiological or cognitive changes in response to treatment*
- Human clinical studies of addicted persons that measure the effectiveness of new treatments that are *emerging as a result of current neuroscience research*

### 4. Psychiatric genomics

- Twin studies
- Linkage analysis
- Association studies
- Endophenotypic study of genomic subpopulations

Each research approach that we describe has a number of investigative strengths and limitations that affect how the information that it provides could and should be used to improve the understanding and treatment of addiction. This is discussed further in the ethical and policy analysis of addiction neuroscience (see pp. 108-30).

### **Studies of Addictive Drugs in Animals**

The study of the acute and chronic use of addictive drugs in animals provides a powerful tool for understanding how drugs act on the brain to produce addictive behaviours. These studies include: the acute effects of drugs on sedation and arousal; chronic effects typical of addiction, such as withdrawal, tolerance, excessive use, and reinstatement of self-administration.

Animal studies are particularly useful in investigating molecular and neuropharmacological phenomena, such as the pharmacology of addictive drugs (i.e. binding affinity, metabolism and transportation), molecular targets and their genetics,

and the reinforcing capacity of different addictive drugs. Animal models of human addiction also enable researchers to localise the neural sites of action of addictive drugs, as well as the neurocircuitry of reward, learning and memory, and other learning processes involved in addiction (e.g. stress, anxiety). Increasingly, animal studies are becoming a particularly powerful tool to study genetic factors that increase the likelihood of addictive drug use and the development of addiction.

Animal studies possess a number of distinct advantages to human studies. First, it is ethically permissible to perform studies on animal subjects, such as neurosurgery and dissection that would be ethically impermissible in humans. Second, the short reproductive cycle of animals such as mice and rodents, enable scientists to conduct relatively inexpensive trials on large numbers of animals that can identify pharmacological and neuroanatomical changes in the brains of developing animals. Third, the genetic modification of mice (e.g. gene knockout or over-expression at particular times and locations during development) enables researchers to obtain a detailed understanding of the molecular genetics and neuropharmacology of addiction in a developing organism in ways that would be impossible in humans. These studies can also illuminate the role of genetic predispositions to a drug addiction. Fourth, animals can also be used to study some neuropsychological and cognitive aspects of addiction, such as effects on memory and learning (e.g. conditioned place preference), behavioural sensitisation to drug effects, and reinstatement of drug use.

While animal models of addiction have helped scientists to elucidate the neurophysiological mechanisms of addiction-like behaviours in some animals, there are uncertainties about how the addictive phenomena in animals relate to addiction in humans. Animal studies are highly controlled and there are significant evolutionary, neurophysiological and cognitive differences between animals and humans (e.g. Geyer and Markou (1995), Koob (2000), Littleton (2000), and Epstein et al. (2006)). It is widely accepted that animal models of addiction have a high degree of predictive and face validity for preclinical testing of new treatments of addiction. There is, however, considerable doubt about whether animal models of addiction fully represent the cognitive aspects of human addiction, such as craving and impaired impulse inhibition and executive control (Geyer and Markou, 1995; Epstein et al., 2006), and therefore directly applied to the human condition.

## **Studies of Addiction in Humans**

Human neuroscience research is required in addition to animal models in order to provide a complete understanding of addiction. Ethical limitations on human neuroscience research require that researchers must use a number of specialised research approaches in studying addiction. Humans are able to respond to more specific and complicated cognitive or behavioural tasks than animals and also to report on their own subjective experiences of drug effects and addictive phenomena, such as craving and loss of control. This greatly increases the range of approaches that are available to neuroscientists and the types and complexity of addictive phenomena that need to be explained. Consequently, there is a greater degree of specialisation in approaches to the neuroscientific study of human addiction.

While researchers from different disciplines (psychology, neuroscience, psychiatry etc) are increasingly collaborating with researchers from other neuroscientific fields, there is still a large degree of specialisation within human neuroscience research which is reflected in the following classification of human neuroscience addiction research. We have classified human addiction neuroscience research into 3 categories, based largely on the difference in tools that they use to study, and the techniques that they use to study them:

1. Human neuropathology – the genetic, molecular and cellular study of human tissue and cell culture
2. Cognitive neuroscience – neuropsychological study of behaviour and brain function in humans participants
3. Psychiatric genomics – genomic and molecular study on behaviour in humans participants

### *Human Neuropathological Studies*

The neuropharmacological and neuropathological study of addiction often involves molecular and cellular studies of post mortem neural tissues taken from addicted individuals after their deaths. These studies enable researchers to assess the effects on brain chemistry and structure of years of chronic drug abuse. These studies involve molecular and cellular staining techniques to identify changes in neural tissue. Such research can be slow and expensive to conduct because of the difficulties in collecting post mortem tissue samples, and the challenges in controlling for the length and severity of drug use, the effects of polydrug abuse, other life experiences (e.g. injury, infectious diseases, diet etc) and individual differences in behaviour that may have preceded drug use. These techniques do, however, allow

for a more accurate analysis of the pharmacological and neuronal effects of drug use. Pathological studies may also be performed using other human tissues and cell cultures.

### *Cognitive Neuroscience*

With the advent of non-invasive imaging techniques, such as fMRI, PET, SPECT and EEG, neuroscientists have been able to identify structural and functional changes in the neurochemistry and neuroanatomy of addicts' brains in response to acute and chronic drug use. These tools can also be used to study in non-addicted individuals the neurophysiology of basic cognitive processes that are often co-opted in addiction (e.g. decision making, learning and memory). In these studies the brains of subjects (often including comparison groups of addicted, at risk, and non-addicted subjects) are visualised using one or more imaging techniques. These imaging methods identify changes in brain structure and function that are either associated with chronic drug use, or that occur in response to the administration of a drug. Often investigators use a combination of neuropsychological approaches (tests of cognition or behaviour, and neuroimaging) to study correlations between the brain's neurocircuitry and neurochemical signalling and changes in behaviour and cognition. These techniques have the advantage over traditional neuropathological techniques in enabling researchers to exert greater control over variables than is possible in neuropathological studies and to study the much larger samples of subjects needed to detect smaller effects. Researchers are also able to measure important cognitive and functional capacities that are not possible in post mortem studies.

Increasingly, these studies are performed on a subpopulation of subjects, such as those with a particular genomic profile. This is an increasingly significant area of research as it enables researchers to identify subgroups within an addicted population who possess a common neuropsychological trait (often called an *endophenotype* or *intermediate phenotype*). These studies may eventually enable researchers to identify subpopulations who will respond better to particular treatments (see below).

### *Psychiatric Genomics*

Neuropsychological and pharmacological studies of addiction in humans are often complemented by molecular genomic studies which screen populations or families of human subjects to identify genomic sequences, genes and their molecular products that may be involved in the development of addiction, or that may predict response to

treatment, maintenance of abstinence or susceptibility to relapse. These are referred to as genetic or molecular epidemiological studies of drug use and addiction. These studies increasingly form an integral part of scientific research into the neurobiological basis of addiction. Twin studies have established a substantial contribution of genetics to addiction risk. Now linkage and association studies are seeking to identify genes or genomic loci that are specifically associated with addiction risk and treatment outcome.

An increasing emphasis in both genetic and neuroscience research is to study neurophysiological and cognitive changes within subpopulations who have a particular genomic profile. This approach has the potential to identify neurophysiological endophenotypes that can be replicated within genetic subpopulations (Caspi and Moffitt, 2006). This approach which is often referred to as *psychiatric genomics* (or *genetics*), may also be useful in identifying genetic subpopulations of addicted individuals who respond better to particular types of treatments, an approach referred to as *pharmacogenetics* or *pharmacogenomics*.

### ***Inclusion/exclusion Criteria***

As described above, it can be difficult to clearly and simply define the limits of neuroscientific study of addiction. Below we provide some clarification of the types of studies that were included or excluded in this review, and justification for their inclusion or exclusion.

This review of current addiction research in Australia focuses narrowly on basic neurobiological research of addiction, where this includes both genetics and neuroscience. Our focus includes those working on basic addiction research using animal models, neuroscientific research on human subjects, whether that be using anatomical, genetic, molecular, or pharmacological, neurophysiological or neuropsychological methods.

We have found that it can be difficult to distinguish neuroscientific research from traditional clinical studies that evaluate the effectiveness of a treatment on addicted individuals or the prevalence of certain addictions or health outcomes within specific populations. Many human addiction studies assess the effect of different treatments or neurobiological interventions on some neurobiological outcome (e.g. pharmacological, neurological or cognitive). Neuroimaging studies also often involve

the use of subjects who are being treated for drug addiction in order to understand the neuropsychological effects of chronic drug use on brain and behaviour.

We excluded from this review individuals in traditional addiction research, such as individuals working in drug and alcohol treatment evaluation or epidemiological research (e.g. population health studies). We have also excluded studies that simply evaluate the effectiveness of drug treatments for addiction (e.g. retention rates, illicit drug use during treatment, and relapse to drug use after treatment). Such studies are often conducted at treatment research centres (e.g. Turning Point). Testing neuroscientific theories of addiction are not an integral part of such studies, although their results can have implications for neuroscientific explanations of addiction. Nonetheless, they have not been included because such a broad conception of neuroscience would dilute our analysis of core approaches to the neuroscientific investigation of addiction. We however did include clinical research on novel medical interventions that derive from recent neuroscientific or genetic research of addiction, or that measured some neurocognitive change in response to treatment.

Our review also excluded individuals working in traditional observational research of addiction (e.g. psychological questionnaires, social science, epidemiology), unless this research was based on or tested neurobiological theories of addiction. For example, we included epidemiological research that also collected DNA with a view to studying polymorphisms that were correlated with drug use and addiction, or some psychiatric or behavioural characteristic relevant to addiction.

A greater challenge was presented by cognitive studies that used psychological tasks to probe or measure activity in specific neural circuits without physically measuring activity in these circuits. For example, the Iowa gambling task is believed to probe prefrontal cortical activity, and performance on it has been used to understand the neurocognitive behaviour of addicted individuals (Bechara, 2005). The results of these studies have significant implications for subsequent neuroimaging and neuropsychological studies which often include these tests. Cognitive research that engaged with neuroscientific theory or knowledge, or could be considered as *cognitive neuroscience*, has been included in this audit, even when it does not physically measure brain function or visualise the brain.

There is a high degree of comorbidity of drug addiction and other psychiatric disorders. Often the effects of drug use may be studied in relation to research on

other psychiatric disorders. Given the importance of research on comorbid psychiatric conditions in understanding the aetiology of mental illness and in treating them, we included studies of other psychiatric disorders where comorbid substance abuse was involved (e.g. McConchie M., Hides L., Lubman D. I., Proffitt T. M., McGorry P. D., Berger G. E. Substance use in first episode psychosis: Prevalence and relationship to psychopathology. *Schizophrenia Bulletin* 2005 31: 190-1.).

A member of the research team (AC) manually sorted through the library of addiction publications to ensure that only those meeting the remit were included. The researcher was blind to the authors and research group during this process. Of the 722 articles initially identified, 422 articles met our exclusion/inclusion criteria. This final publication database was then used in order to quantify neuroscience research on addiction, according to the categories just described. A list of the publications contained in the Endnote library is provided in Appendix 2.

Each article was also labelled with a tag that identified the research group for each of the article authors of interest. A code for each group (see Appendix 1 for the codes) was placed in the *caption* field of the Endnote library for each author to identify them their research group. These tags were then used to quantitatively analyse each research groups publications (see below). Each publication was only counted once for each group. For example, if there were 3 authors from the same research group, the article was only counted once for that group. However, if the article was also authored by a research from another group, it would also count as one publication for that group as well. The reason for doing so was to determine the research output of each research group, and not for each particular researcher. The results of this analysis are below (see Figure 14.).

## ***Results of Quantitative Analysis of Australian Addiction Neuroscience Research***

### **Animal vs. Human Research Studies**

The first step in the analysis was to separate the publication database into “animal” and “human” studies. We identified animal studies by searching: the *taxonomic* field of the addiction publication database with the term “nonhuman” (for articles retrieved via BIOSIS Previews); and the *label* field with the term “animals” (for articles retrieved from PubMed). These articles were then manually examined to ensure that the search strategy correctly segregated the articles into the appropriate groups. Several



articles were found in both the human and animal groups that were incorrectly categorised, and had to be reassigned. Several articles were also deemed to involve both human and animal research, and were therefore recorded in both groups. This identified 180 animal studies (approx. 42% of addiction research) and 247 human studies (approx. 58%). See Figure 12. The human studies were then categorised further into 3 subcategories as described above.

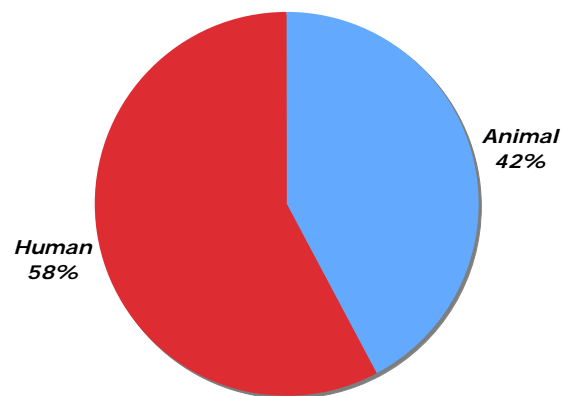


FIGURE 12. HUMAN VS. ANIMAL ADDICTION NEUROBIOLOGY RESEARCH IN AUSTRALIA

### **Human Studies**

It was not possible to identify any collection of search terms that would accurately and consistently segregate all human studies into one of the three categories (neuropathology, cognitive neuroscience and psychiatric genomics). This classification was therefore done manually. A member of the project team (AC) went through all records in the addiction database that involved human research to separate them into one of the three categories. Each publication was classified by the title if possible. If it was not possible to confidently classify the publication by the title alone, the abstract was used. If it was still not clear, the complete article was retrieved and classified. The reviewer was blind to the author and research group during this process. Of the 247 human studies, 141 were considered cognitive

neuroscience, 56 neuropathology, and 44 psychiatric genomics. A comparison of the amount of research performed in each of the 4 types of addiction neuroscience defined, as measured by publication output, is depicted in Figure 13. Each group of articles were segregated into separate Endnote libraries for analysis.

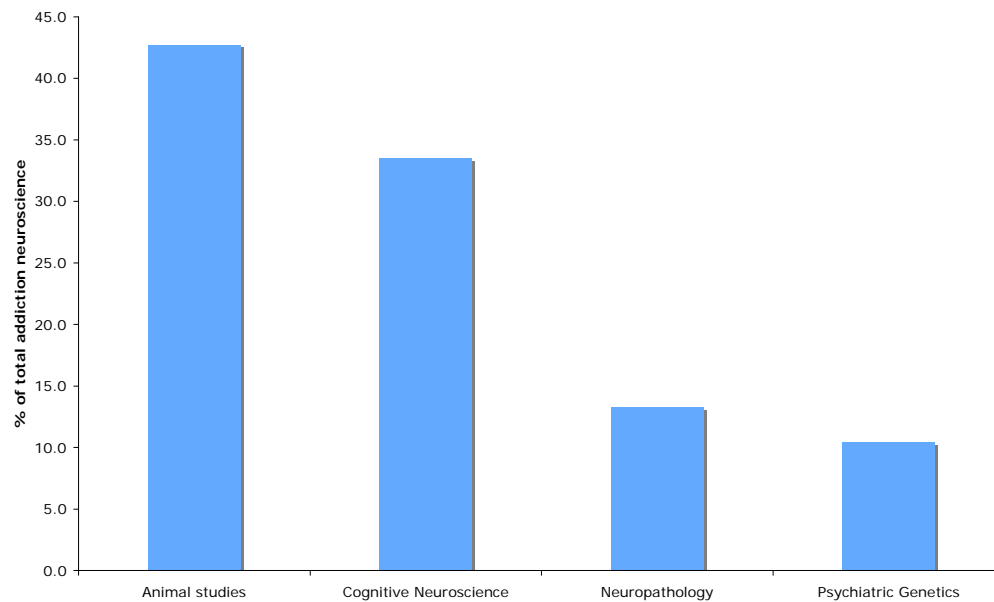


FIGURE 13. TYPES OF ADDICTION NEUROBIOLOGY RESEARCH IN AUSTRALIA

An analysis of publications in each research category in the last 3 years showed that there had been very little change in the type of research being conducted in Australia over this time (data not shown).

It must be noted that the number of animal studies may be slightly elevated relative to the human studies because the animal studies may also include basic neuroscience studies that would have been excluded from the analysis of human studies. The distinction between measuring the acute effects of drugs in the context of addiction and basic neuropharmacology research is not as clear as it is in human research. Addictive drugs are an important tool in studying the neurochemical basis of animal behaviour because it allows researchers to manipulate endogenous neurochemical systems.

## Research Group

Publications for each of the 60 researchers were tagged with a code that associated them with their research group. This enabled us to quantify the number of publications arising from each of the research centres. The numbers of publications in the last ten years at each research group are presented in Figure 14.

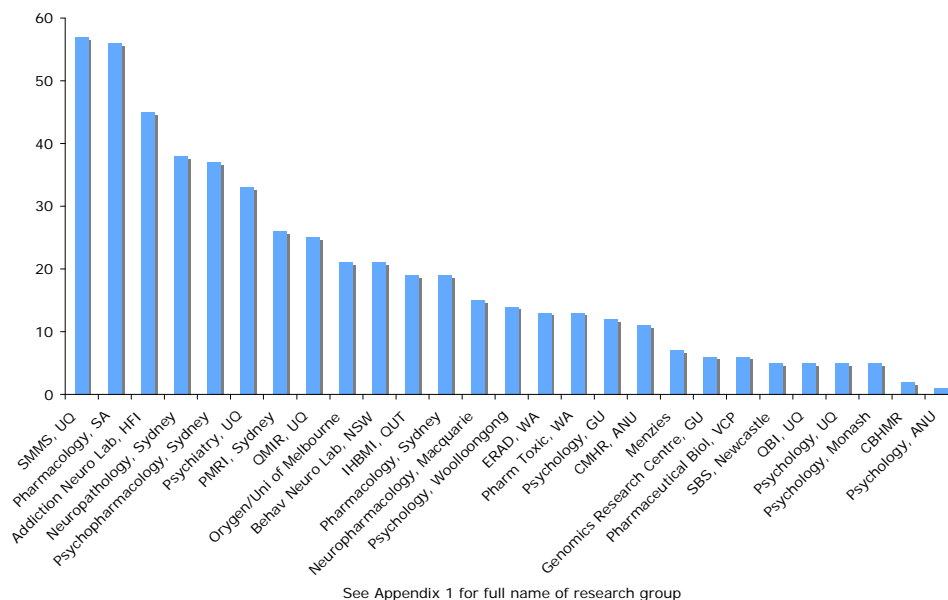


FIGURE 14. QUANTITATIVE ANALYSIS OF ADDICTION NEUROBIOLOGY RESEARCH BY RESEARCH GROUP (SINCE 1997).

This data represents publications over a 10 year period. It is possible that they this figure may not represent the current research activities of these centres. We therefore quantified the number of publications in the last 3 years (see Figure 15).

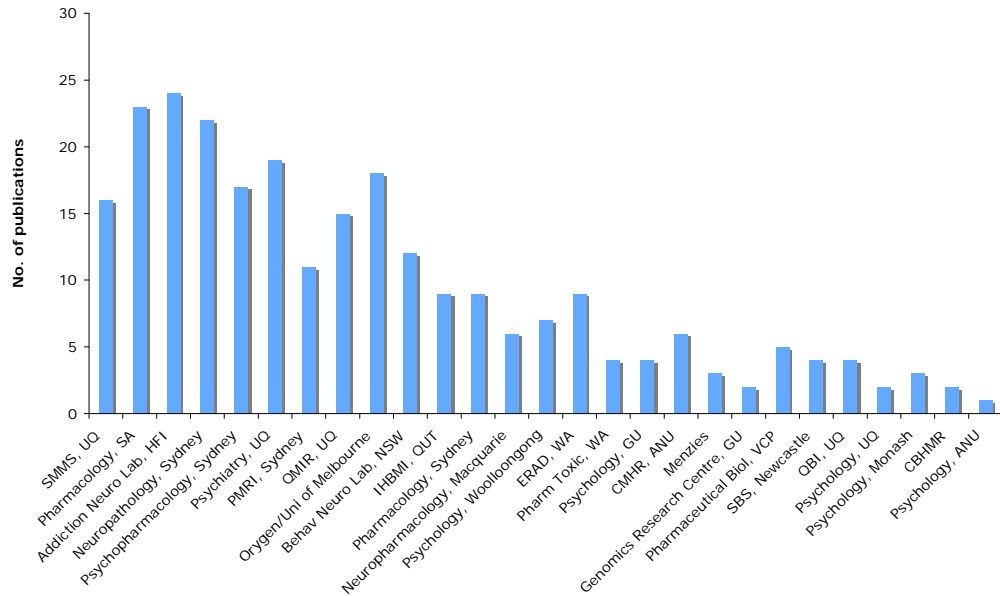


FIGURE 15. QUANTITATIVE ANALYSIS OF ADDICTION NEUROBIOLOGY RESEARCH BY RESEARCH GROUP (SINCE 2005).

### Addictive Drugs Studied

By searching the addiction neuroscience publication database, it was possible to quantify the amount of research on each of the major drugs of addiction. The following search terms were used to identify each class of addictive drug:

<i>Class of drug:</i>	<i>Search terms:</i>
Opioids	Opiate, opioid, morphine, heroin, methadone, LAAM
Psychostimulants	Stimulant, cocaine, amphetamine, PMA, MDMA, ecstasy
Nicotine	Tobacco, nicotine
Alcohol	Alcohol, ethanol
Petrol	Petrol, solvent, toluene
Cannabis	Cannabis, THC, marijuana,
Other	Benzodiaz, diazepam, kava,

These search terms were entered into the *title* field. Preliminary searches established that searching other fields, such as abstract, yielded too many articles. The results of this analysis are presented in Figure 16.

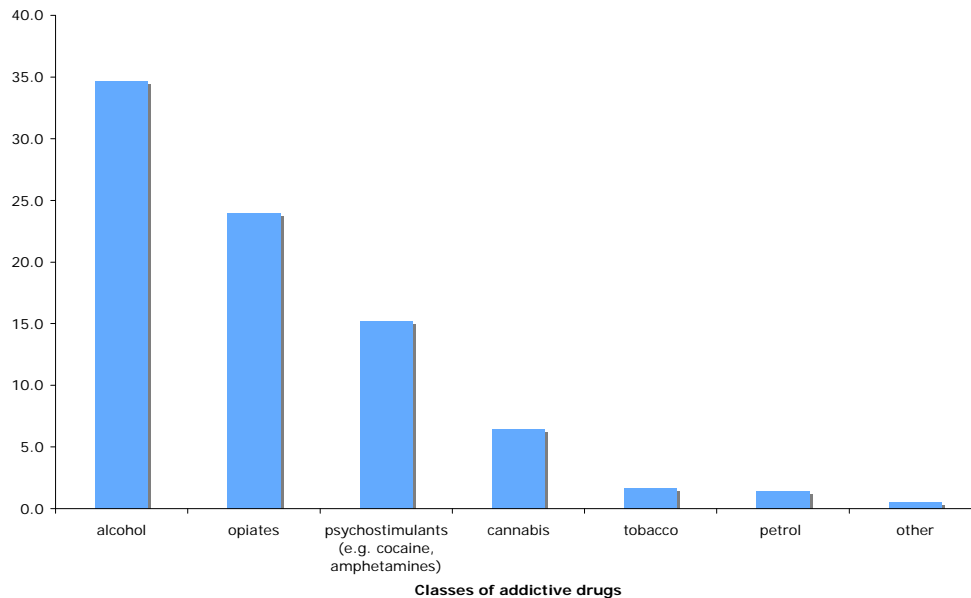


FIGURE 16. QUANTITATIVE ANALYSIS OF ADDICTIVE DRUGS RESEARCHED IN AUSTRALIA (SINCE 1997).

### **Quantitative Analysis of Publication Impact**

In addition to the amount of addiction neuroscience research conducted in Australia, we also wished to quantify the impact of this research internationally. To this end we collected the impact factors listed by the *Web of Science* (Thompson Scientific) for each of the journals in the publication database. The Web of Science impact factors provide the widest coverage of journals available. There were a small number of articles that were published in journals where no impact factor was recorded, and these articles were excluded from the analysis. For ease of analysis we used the most recent (2006) impact factor data. There are some limitations with this approach which will be discussed below.

The average impact factor was calculated simply by adding the impact factor for every publication and dividing by the number of publications. This figure reflects the impact of the research that each research group published (see Figure 17). A limitation of the average impact factor is that it does not take into account the quantity of publications. For example, a researcher who publishes one article in a journal with an impact factor of 20 will have a higher mean impact factor than a researcher who publishes 100 articles in a journal with an impact factor of 10. The impact of a single high impact paper can be seen in the figure for the Department of Psychology, University of Wollongong where a single Lancet paper with an impact factor >20 greatly skewed the result.

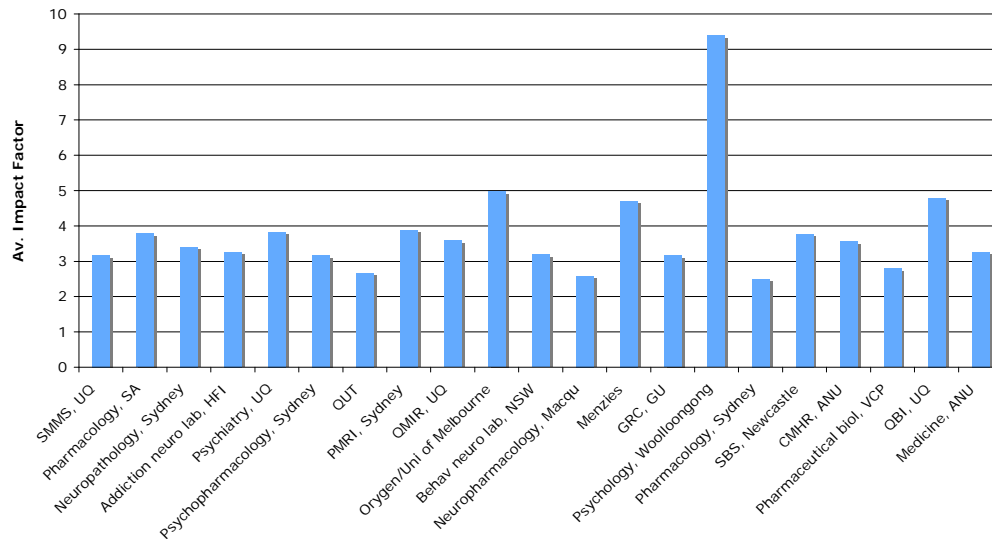


FIGURE 17. AVERAGE IMPACT FACTOR FOR EACH RESEARCH GROUP IN AUSTRALIA.

To take this into consideration, we also calculated the sum of the impact factors for each publication. This reflects both the impact that the research has and the number of publications. See Figure 18.

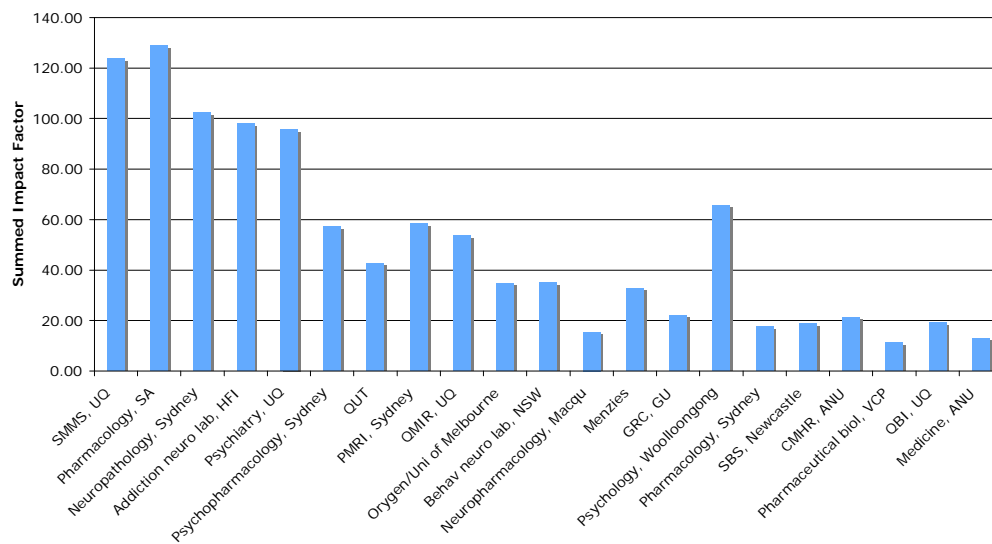


FIGURE 18. SUMMED IMPACT FACTOR FOR EACH RESEARCH GROUP IN AUSTRALIA.

## 4. Discussion

The majority of addiction neuroscience research in Australia has been conducted on human subjects (52%). This contrasts with the situation in the US where addiction neuroscience research is dominated by studies in animals. We were able to identify 28 research groups working on addiction neurobiology in Australia, comprising 61 researchers. Of these, only 6 groups could be considered to working specifically on addiction neuroscience (publishing more than 30 articles over the 10 year period; Figure 14). Looking at more recent data, it appears that there are 7 groups that could fall into this category, demonstrating an increase in interest in the study of addiction neuroscience (publishing more than 3 articles per year based on the last 3 years; Figure 15):

- Addiction Neuroscience Laboratory, Howard Florey Institute;
- Drug Dependence Laboratory, University of Adelaide;
- Psychopharmacology Laboratory, University of Sydney
- Orygen Research Centre, University of Melbourne;
- Department of Psychiatry, University of Queensland (which has a dedicated Addiction Psychiatry research centre);

- and the two neuropathology research groups – Neuropathology Laboratory, University of Sydney and the School of Molecular and Microbial Sciences, University of Queensland

In addition, there are two other addiction neuroscience research-intensive groups that are worth highlighting:

- Behavioural Neuroscience Laboratory, University of New South Wales, and
- School of Biomedical Sciences, University of Newcastle

These groups have only recently become involved in addiction neuroscience research, and therefore their work is not yet reflected in the publication data. The leaders at these groups have published a number of high quality articles in the last two years in high impact journals which have already received a number of citations. The leaders of these groups have also recently secured a large peer-reviewed NHMRC grant (2008) in addiction neuroscience research.

This recent increase in addiction neuroscience research is consistent with international trends in addiction neuroscience research. As we had hypothesised, most of the published addiction research was conducted at a small number of dedicated research centres, with a large number of researchers publishing on addiction working within traditional psychological and biomedical university schools that have more than one focus.

Our quantitative analysis of addiction publications over the last 10 years found similar amounts of studies in animals and humans, with a slight leaning towards human research (58%). The genetic, pharmacological and behavioural studies of animals, such as mice and rats, made up a significant percentage of addiction neuroscience research in Australia when compared to the 3 human fields, accounting for 42% of the work published. There were 9 groups identified working on addiction neuroscience in animals. The groups at The University of Adelaide and the Addiction Neuroscience Laboratory at Howard Florey Institute were two of the most active research groups analysed across most measures (number of publications, summed impact factor). In the last 3 years, the Psychopharmacology Laboratory at the University of Sydney also produced significant research in this area, as has the Behavioural Neuroscience Laboratory, University of NSW. This appears to be consistent with our review of the international literature, where animal studies of addiction are given a significant focus.



There are a slightly more groups working in cognitive neuroscience (13), producing slightly fewer publications than the animal research. This is not surprising given the significant resources and infrastructure required to undertake this type of research. Also, many of these groups are made up of one or two researchers operating within psychology and medical departments, forming collaborations with other researchers in similar situations, on other departments or different universities.

The Psychiatry Department at the University of Queensland has produced the most publications in this area, reflecting their specialisation in this field, and access to addicted participants. An analysis of publications limited to the last 3 years, however, shows that the ORYGEN Research Centre group at the University of Melbourne is increasing its focus on addiction research. Previously they had been focussing more on research on psychosis and schizophrenia. However, with the emergence of the SURRF (Substance Use Recovery Research Focused) centre specialisation, there has been a significant increase in research on addiction. This is a significant area of research in the US, particularly at NIDA, but it is an expensive area of research that US researchers are better funded to do.

The most unexpected result from the analysis on the addiction neuroscience research in Australia was the amount of neuropathological research that is conducted. The two groups identified working in this area (School of Molecular and Microbial Science, The University of Queensland and the Neuropathology Laboratory, The University of Sydney) produced over 15% of the total of Australian addiction neuroscience research. This is also a resource intensive area that requires access to post mortem brain tissue and probably reflects access to a large brain tissue resource (Prof Clive Harper, head of the Neuropathology Laboratory, runs Australia's Brain Bank facility for neuroscience research). This is an area in which Australia appears to have unexpected strengths that may provide a unique resource. These results suggest that Australia is a world-leader in the field.

Psychiatric genomics was found to be the smallest area of research in Australia. There were 4 groups identified undertaking research on the genetic basis of addiction. Most research in this field was undertaken at the Genetic Epidemiology group, Queensland Institute of Medical Research, reflecting their expertise and access to the Australian Twin registry, a unique resource for the genetic study of disorders in the general population. Psychiatric genomics is an area that is increasing in importance, as outlined by the recent Nature Neuroscience paper by Caspi and

Moffitt (2006). They argue that future research will need to examine genetic differences that underpin neurocognitive and psychiatric characteristics. Researchers at the Genomics Research Centre, Griffith University and The Queensland University of Technology are beginning to undertake such work. This is an area in which Australia has the capacity to make a more significant contribution, particularly given the unique resources and expertise of the QIMR group.

Another area of research that is increasing in influence in addiction research internationally is computational modelling of neuronal behaviour (Schultz et al., 1997; Montague et al., 2004; Schultz, 2007). This research is helping neuroscientists to understand the role of dopamine in learning and memory, and to refine neurobiological theories of addiction. We were unable to find any researchers in Australia working in this area in addiction. This was confirmed by conversations with Australian experts working within neuroscientific computational modelling. Australia does have expertise in computational modelling of neuroscience and there are individuals working on modelling neuronal behaviour in other psychiatric disorders. This is an area which Australia's research efforts in addiction could be enhanced.

An analysis of the average impact factor shows that Australian research in addiction neuroscience is highly regarded, with most groups' average impact factors between 3 and 5 (considered to be a significant impact within the fields of neuroscience, molecular biology and psychiatry). As discussed above, while the average impact factor provides a guide to the overall quality of publications, it does not take the number of publications into account. The summed impact factor provides a more accurate measure of this. These results confirm the fact that the most highly influential addiction research is being conducted within a small number of research centres:

- School of Molecular and Microbial Science, University of Queensland; and the Neuropathology Laboratory, University of Sydney (Human neuropathology)
- Addiction Neuroscience Laboratory, Howard Florey Institute; and the Drug Dependence Laboratory, Discipline of Pharmacology, University of Adelaide; Psychopharmacology Laboratory, University of Sydney (Animal studies)
- Department of Psychiatry, University of Queensland; and School of Psychology, University of Wollongong (Human cognitive neuroscience)
- Queensland Institute of Medical Research, University of Queensland (Psychiatric genomics)

When only the last 3 years are considered, the ORYGEN Research Centre, University of Melbourne (Cognitive neuroscience) and the Behavioural Neuroscience Laboratory, University of NSW (animal studies) also fall into this category.

It must be noted that there are a number of limitations with analyses that rely solely on impact factors from the Web of Science. Firstly, our analyses applied impact factors from 2006 to publications since 1997. These figures do shift over time, and the figure now may not reflect the impact of the journal at the time an article was published. Secondly, the Web of Science impact factors do not take into account differences of impact within specialised field categories or for particular populations of readers (e.g. Australian journals). For example, a publication may occur in a journal that is the leading publication within a particular field, but still receive a lower impact factor compared to journals with wide readership (e.g. medical journals such as *The Lancet*). Rankings of journals within particular fields (tiered journal lists) are available and would provide a more accurate reflection of an article's impact within its field. However, given the rather narrow field of journals published in, it is unlikely that this would impact too heavily on this analysis. This is also confirmed by the average impact factor analysis which found that most publications fell within a narrow range (with a couple of exceptions).

The analysis of which addictive drugs are researched found that alcohol research dominates the field (approximately 35%). This reflects the significant problems posed by alcohol abuse and the focus of the two neuropathological groups on the effects of alcohol abuse on the brain. Given the enormous mortality associated with chronic alcohol abuse, it also reflects the brain tissue resources available at the brain banking centre. Opiate research is also highly represented. This is consistent with the international field where opiate addiction is often considered the prototypical addiction. Research of other addictive substances is more limited. Psychostimulant research only makes up 10% of Australian addiction neuroscience. This is a small figure when compared with the US which probably reflects the much larger problem with cocaine abuse in the US. There is, however, a significant problem with amphetamine abuse in Australia (Degenhardt et al., 2010), suggesting that more investment in neuroscience research in this area may be warranted. Research into tobacco addiction in Australia was surprisingly small given the

enormous disease burden that it causes, and the number of people who are addicted. This is an area where neurobiological research could be increased.

Our analysis also found that there was very limited research on the effect of drug abuse and addiction in indigenous populations (<2%; data not shown). Given the enormous burden affecting many indigenous communities as a result of alcohol and other drug abuse, this is an area of research that deserves further attention.

## Recommendations

International neuroscience research on addiction is an intellectually exciting field that promises to very substantially increase our understanding of the effects that drug use has on the human brain and of the role that neural processes play in the development and persistence of addictive patterns of drug use. As this review shows, neuroscience and genetic research of addiction offers the very real potential of providing more effective treatments to reduce the burden of addiction, assist individuals in reducing and stopping harmful drug use, and more speculatively, preventing or reducing the incidence of addiction, via a range of intervention options, including pharmacology, psychotherapy, better targeted treatment and clinical guidance, education, and other social initiatives.

There has been unprecedented interest and investment in neurobiological research of addiction internationally, with a number of special issues in leading journals in recent years dedicated to neuroscience and genetic research of addiction, e.g. *Nature Neuroscience*, *American Journal of Psychiatry*, *Archives of General Psychiatry*, *Biochemical Pharmacology*, *Current Opinion in Neurobiology*, and the *British Journal of Pharmacology*. The majority of this research has been undertaken in the USA with funding from two major research institutes (NIDA and NIAAA) which have been dedicated to elucidating the neurobiology of addiction for over 3 decades. Similar research is increasingly being done in the United Kingdom and Europe. The audit of Australian research on addiction neuroscience included in the document indicates that world class research is also being done in Australia.

There are as yet a relatively small number of Australian research groups working primarily in addiction neuroscience. Many of these are working on animal models of addiction. There are a number of research groups who do some work in this field while primarily working in other related fields. This includes: genetic epidemiologists who undertake work on the genetics of addictive disorders while studying the genetics of various forms of behaviour disorders; researchers undertaking neuroimaging studies of major mental disorders, in particular schizophrenia, who also do studies of the brains of persons with different forms of addiction, comorbid addiction, and the role of drug abuse in the development of mental illness (e.g. psychosis); addiction researchers who are interested in assessing the genotypes of

addicted persons or in measuring brain function to see how this may assist in diagnosis or treatment selection; and clinicians who are interested in evaluating new treatments that are derived from or suggested by neuroscience research on addiction.

It is in Australia's interest to develop work in this field. Failure to do so will leave Australia dependent upon work done elsewhere. It will also make it more difficult for Australian researchers to critically evaluate the quality and relevance of work that is done elsewhere. In the longer term, it would put at risk the high reputation that Australian addiction researchers have achieved over the past several decades.

There is also a clinical and public health need for Australian-funded neurobiological research on addiction.

- (1) Rates of drug use and addiction in Australia are reasonably comparable to those in other Western countries, such as the US and UK but there are issues that are unique to Australia (e.g. specific patterns of drug use, social, medical and public health institutions, cultural differences, government and regulatory networks). These can affect the types of treatments that will be required, their effectiveness and how they will be best provided. This requires strategic research in Australia to test the applicability of treatments and approaches developed in the Europe, the UK and USA .
- (2) The social political and cultural context in which research is conducted can have a significant impact upon how the results are interpreted and their impact on policy. There are differences, for example, between the addiction research agendas in the US and Europe, and a significant difference between how researchers in these two regions describe the results of addiction neuroscience research. It is imperative that Australia undertake its own research so that the interpretation of this research is informed by Australia's social, political and public health needs.
- (3) Australia needs to build expertise in neuroscience research on addiction and other mental disorders. A report by the Prime Minister's Science, Engineering and Innovation Council (PMSCEI) found that the burden of mental illness presents a significant threat to Australia's health and economic future (Independent Working Group on Brain and Mind Disorders, 2003). Given the significant comorbidity associated with drug abuse and addiction, Australia needs to invest more in research on addiction and other mental disorders.

Our report indicates that there is considerable capacity to expand the current Australian research effort in addiction neuroscience. This should be done in ways that would build on Australia's international strength in the field of addiction research. This will require increased research funding work through the traditional peer-reviewed mechanisms of the Australian Research Council and the National Health and Medical Research Council. This may involve:

- (1) Increased NHMRC investment, or increased priority being given to addiction neuroscience research, with a focus on increasing opportunities for human neuroimaging studies, an area in which Australia has good capacity for research into serious mental disorders, but in which addiction researchers have struggled to secure funding.
- (2) Funding efforts to foster collaborations between clinical and epidemiological; addiction researchers and neuroscience researchers working in each of the major fields of addiction neuroscience, that is, animal models of addiction, human neuroimaging studies of addicted persons. It is now widely recognised in the scientific community that further advances our understanding of addiction and our ability to treat it will require an integrated approach that aims to synthesise research from a number of fields (van den Bree, 2005; Goodman, 2008).
- (3) Giving an increased but not excessive emphasis to translational research into the development and testing of new drug treatments suggested by addiction neuroscience research: bridging the gap between lab bench and bedside.
- (4) Developing a greater awareness of research in the clinical community, and to fostering more integrated and collaborative relationships between the research and clinical communities, in order to develop the most clinically appropriate and effective treatments of addiction.
- (5) Fostering a wider public, professional and political recognition and acknowledgement that addiction is a public health issue that can and should be treated effectively.
- (6) Anticipating and preventing potential misuses and misrepresentations of neuroscience explanations of addiction, such as those outlined in the report, via strategic funding of research on the ethical and social implications of potential applications of addiction neuroscience. Among its aims would be moderating media enthusiasms for more speculative uses of this research (e.g. preventive vaccination against addiction) and increasing policy-makers' and the public's understanding of addiction neuroscience and its applications.

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## Glossary

Abstinence	The cessation of drug use after an extended period of use of an addictive drug. Abstinence in a dependent drug user may lead to the experience of withdrawal symptoms.
Acetylation	An epigenetic process whereby an acetyl group is added to the histone residues reducing the electrostatic interaction between histone proteins and DNA, which is thought to loosen the chromatic structure making the DNA more accessible to transcriptional regulators and therefore increase DNA transcription.
Addiction	The repetitive engagement in an activity, such as drug use, gambling or eating, despite the negative consequences that it causes. Addiction usually involves intense craving for the addictive activity and an impaired ability to control use. These aspects of addiction are sometimes referred to as <i>psychological dependence</i> . Addiction also often involves the development of <i>tolerance</i> towards the drug of abuse, and symptoms of <i>withdrawal</i> upon cessation of use. This is often referred to as <i>physical dependence</i> .
Agonist	A substance which binds to the same receptor as the target drug (in this case the drug of addiction) producing the same or similar pharmacological effects.
Alleles	A member of a pair or series of different forms of a gene, that are often responsible for hereditary variation.
Allostasis	The process of maintaining homeostasis through physiological change. In addiction allostasis is the process of maintaining apparent reward function stability through changes in brain reward mechanisms.
Amygdala	A small group of neurons in the <i>limbic system</i> of the brain that is involved the processing of emotional information, learning and memory.
Anhedonia	The inability to experience pleasure.
Anterior cingulate gyrus	The front part of the cingulate cortex, a region along the medial surface between the two cerebral hemispheres, that is involved in decision-making and particularly the regulation of emotional impulses to act.
Associative Learning	A learning process in which a new response becomes associated with a particular stimulus.

Antagonist	A substance which binds to the same receptor as the target drug (in this case the drug of addiction) preventing it from having its usual effects.
Anti-reward Pathway	A pathway in the brain that is hypothesised that limit reward triggered by excessive activity in the reward system. It is most often associated with systems involved in affect regulation such as the corticotropin releasing factor stress system.
Autonomy	(Greek 'self' and 'law') The capacity for self-government. Agents are autonomous if their actions are truly their own.
Behavioural Sensitiisation	The progressive increase in motor stimulatory effects of a drug following repeated administration. The development of behavioural sensitisation is believed to represent a shift to compulsive drug use. It is also referred to as <i>locomotor sensitisation</i> .
Buprenorphine	A drug that is a <i>partial agonist</i> of opioid receptors. It is often used in the treatment of opioid dependence, either as a form of <i>maintenance</i> , or as an aid to <i>withdrawal</i> . It can also lead to dependence.
Cerebrum	The two uppermost lobes of the brain, that consists of a left and right hemisphere. An evolutionary recent part of the brain that sits above the more primitive parts of the brain, such as the mid and hindbrain. Also often referred to as the <i>forebrain</i> .
Chromatin Remodelling	Biochemical changes in the structure of the chromatin, folded DNA around histone proteins, that influence transcriptional regulation. Chromatin remodelling is an <i>Epigenetic</i> process.
Coercion	The use of force to encourage someone to enter treatment. The type of force used may vary depending on the amount of choice that an individual has. Mild forms include pressure from friends and family; the strongest forms involve detaining individuals in treatment against their wishes.
Conditioned Incentive-learning	The association of reward with a previously neutral stimulus when paired with a naturally rewarding event (e.g. addictive drug use). Conditioned incentive-learning is an important addictive process that underpins behaviours such as conditioned place preference.
Conditioned Place Preference	Animals show a preference for an environment in which they are administered addictive drugs. Conditioned Place Preference is a widely used animal model of addictive behaviour.
Confidentiality	Ensuring that information is accessible only to those authorized to have

access. It restricts the use of personal information about an individual so that it cannot be communicated without their consent. In some professions, access and use to information is often 'privileged', and therefore may not under normal circumstances be discussed or divulged to third parties.

Cortex	The outer mantle of the brain, specifically the cerebrum, which is involved in the highest cognitive functions, such as conscious sensation and movement, language, and decision making.
Craving	An intense and seemingly irresistible desire to experience the effects of drugs
Compulsion	In addiction, compulsion refers to an experience of a strong, usually irresistible drive or desire to consume drugs that is often contrary to one's will.
CNS Depressants	A class of drugs that slow CNS function, and can lead to fatal overdose in large doses from respiratory and cardiac failure.
Cues, or Drug Cues	Events which have the ability to bring up memories that can often trigger emotional responses. Drug cues are those which recall memories associated with drug use that often trigger intense cravings for the drug.
Detoxification	Supervised withdrawal from a drug of addiction that allows the drug to disappear from the brain and body. It is nearly always accompanied by withdrawal symptoms that may be managed using other drugs (medicated) or psychological support (unmedicated).
Dopamine	A chemical in the brain, or <i>neurotransmitter</i> , that is central to the development of addiction. It is found in the regions of the brain that are involved in the regulation of movement, motivation, emotion and reward.
Down-regulation	A process which causes a reduction in the expression of a given gene.
Drug Priming	The use of a small amount of an addictive drug in abstinent addicted individuals that produces intense cravings for the drug that often leads to a relapse to chronic drug use.
Dysphoria	A feeling of being unwell, anxious, depressed and restless.
Endogenous	A chemical or substance produced within the body
Endophenotype	Some measurable biological characteristic of a person that is believed to be influenced by a set of genes, and gene and environmental

	interactions.
Endorphins and Enkephalins	Forms of <i>endogenous</i> opioids: naturally occurring substances in the human brain that bind to the same receptors as morphine..
Epigenetics	The study of non-genetic factors (e.g. environmental events such as chronic drug use) that alter the expression of genes in persistent ways.
Ethics	The study of the concepts involved in practical reasoning: good, right, duty, obligation, virtue, freedom, rationality, choice etc. (Sometimes referred to as the study or formalisation of morality).
Euphoria	A feeling of exuberance, elation and maximum well-being
Executive Control	The cognitive ability to control all other cognitive processes and behaviour. It is considered to be central process in decision-making.
Fatalism	The belief that a set of pre-existing circumstances or events predetermined a particular outcome. It is often used in genetics and biology to suggest a belief that an agent could not avoid a particular outcome, and should not attempt to do otherwise.
fMRI	Functional magnetic resonance imaging (or fMRI) is a brain imaging technique that measures changes in blood flow in order to visualise brain activity during particular tasks.
Forebrain	The largest and most evolutionary recent division of the brain, including the cortex , limbic system and basal ganglia. It is the region of the brain involved in our most advanced cognitive functions.
Frontal cortex	A region of the <i>cerebrum</i> that is involved in our most higher order cognitive functions, such as decision-making and social or moral judgement.
Harm Minimisation (or Reduction)	An approach to the treatment of addiction and drug abuse whose principle aim is to reduce the harm caused by drug use to both the individual and society without necessarily eliminating drug use. Harm reduction is an evidence-based approach towards drug policy, and claims to take no position on the rights and wrongs of using drugs. Needle exchange programs and methadone maintenance are two types of harm reduction programs.
Hedonic Theory of Addiction	A theory of addiction that holds that addicted individuals repeatedly use addictive drugs because of the pleasure that it offers.
Heroin	A synthetic opiate that is the most commonly abused and one of the most addictive illicit drugs.

Heroin Prescription Trials	Clinical trials of the prescription of injectable pharmaceutical heroin for treatment refractory heroin addicts in order to improve health and well being by replacing the use of unsupervised illicit heroin use.
Hippocampus	An area of the brain involved in learning and memory, specifically memory for the facts or details of events, referred to as declarative memory.
Homeostasis	The ability of an organism to maintain internal stability, by adjusting its physiological processes.
Homozygous	A term used to describe when an individual carries two identical copies of a gene (one from each parent) at a particular locus on each of the two chromosomes. An individual who carries two different copies of a gene is said to be <i>heterozygous</i> for this gene.
Hypothalamus	A small, but important part of the brain that maintains many of the bodies internal functions, such as eating, drinking and the regulation of hormones, such as the stress hormones
Human Rights	Protections of <i>human</i> (moral) interests (see rights).
Impulse Inhibition	The cognitive ability to resist strong urges or desires.
Incentive Sensitisation	A theory of addiction that holds that addicted individuals become hypersensitive to drug effects and stimuli or events associated with drug use, that lead to a shift from drug 'liking' to drug 'wanting'. The incentive sensitisation theory of addiction is believed to explain the apparently compulsive patterns of drug use.
Incubation of Craving	The increase in craving in the weeks following abstinence of drug use.
Informed Consent	A process whereby individuals are fully informed about a particular treatment that they are to receive, and where individuals are free to participate or not.
Insula Cortex	A region of cortex that lies at the intersection of the frontal, temporal and parietal lobes that is involved in the process of <i>interoception</i> , or the conscious experience of the body.
Interoception	The conscious experience, awareness or sensation of the body
Intracranial Self-stimulation	An animal model of addiction in which small microelectrodes inserted into the brains of animals are electrically stimulated when an animal presses a lever. When placed in particular regions of the brain, such as the ventral tegmental area and the nucleus accumbens, animals will

	self-stimulate at a high rate.
Liberty	A condition in which an individual has the ability to act according to his or her own will.
Limbic System	A diverse array of densely connected brain regions that are involved in the regulation and generation of our emotions and desires. These regions are also involved in learning and memory.
Locomotor Sensitisation	See <i>Behavioural Sensitisation</i> .
Long-term depression	A molecular adaptation that occurs at the synapse between two neurons that leads to a weakening of the connection between these neurons.
Long-term Potentiation	A molecular adaptation that occurs at the synapse between two neurons that leads to a strengthening of the connection between these neurons.
Maintenance Therapy	The long-term replacement of an abused drug with its agonist in a regulated way to prevent relapse to more dangerous and illicit drug use. The most well known type is methadone maintenance.
Medicalisation	The process whereby behavioural or social problems are understood as medical disorders that should be treated medically, often at the expense of social approaches.
Mesolimbic Pathway	See <i>Reward pathway</i> .
Methylation	An epigenetic process whereby methyl groups are added to the chromatin augmenting DNA transcription.
Motivation	The promotion of an action in response to particular kind of environmental event or object.
Mu Receptor	The primary opioid <i>receptor</i> that mediates the pleasurable effects of both opiate drugs, such as heroin and morphine, as well as endogenous opioids, such as the endorphins.
Naloxone	A potent opioid antagonist that is used to treat opioid overdose, and is included in the drug, <i>Suboxone</i> , to discourage its injection.
Naltrexone	A potent opioid antagonist that binds to the target opioid receptors preventing heroin and other opioid agonists from having an effect. Naltrexone is often used as a form of relapse prevention. Naltrexone is also used to treat alcohol dependence and eating disorders.
Natural Reinforcers	Everyday activities which are reinforcing or rewarding, such as food, sex and relationships. Natural reinforcers also activate the brain's

	reward pathway, but much lesser than addictive drugs.
Neurotransmitter	A chemical produced within the neurons in the brain that carries signals to other neurons, usually by binding to <i>receptors</i> on adjacent neurons at the <i>synapse</i> . They are a type of signalling molecule that also includes other substances such neural hormones.
Nucleus Accumbens	A central part of the <i>mesolimbic reward pathway</i> that encodes information related to the rewarding or reinforcing properties of an event, or drug, and signals its <i>saliency</i> . Nearly all drugs of abuse act upon the nucleus accumbens, thereby reinforcing their use.
Opioid Naiveté	The term given to a condition in which a former opioid addict who has withdrawn from opioid use, loses their tolerance to opioids. Opioid-naive users who return to opioid use are at a higher risk of <i>overdose</i> if they inject their usual dose of opioid.
Orbitofrontal Cortex	A region of the prefrontal cortex involved in the attribution of salience to events, craving and the motivation to use drugs.
Overdose	An acute condition that results from taking too much of a drug. It can cause unconsciousness, brain damage, and death. It is more commonly used in reference to the <i>CNS depressants</i> , such as alcohol and heroin.
Partial Agonist	Drugs that bind to the target receptor of a drug of addiction, partially blocking and partially activating the receptor. They can be used to treat drug dependence (e.g. <i>buprenorphine</i> for the treatment of opioid dependence).
Paternalism	The name given to the position that persons have a right to act in the interests of others without the consent of, or even against the will of, these others. (Sometimes substituted by <i>parentalism</i> ).
PET	Positron emission tomography (or PET) is a brain imaging technique that uses radioactively labelled molecules to visualise brain structure and function.
Pharmacogenomics / genetics	The use of genetic or genomic information about an individual to select the pharmacological or psychosocial treatments that will maximise the chance of successful treatment for that person.
Physical Dependence	A physiological state that is indicated by the occurrence of <i>withdrawal</i> symptoms when regular drug users abruptly stop taking the drug and accompanied by the development of <i>tolerance</i> , requiring higher doses to achieve the same drug effect

Preclinical Trials	The testing of new medical technologies, such as a drug treatment, in animal models in order to gather evidence for conducting human clinical trials.
Prefrontal Cortex	The very anterior of the frontal cortex of the brain, that includes the <i>orbitofrontal cortex</i> and the <i>anterior cingulate cortex</i> . It is considered the highest cortical area in the brain and underlies our most complex behaviours, including personality, social and moral behaviour, executive control and planning.
Privacy	An individual's right to keep their personal information and affairs confidential, and out of public view, or to control who has access to this information and what they can do with it.
Proteomics	The study of the structure and function of all proteins produced by an organism or system, including all post-genomic modifications made to a set of proteins.
Public Interest, the	Refers to <i>competing</i> claims made by a public concerned with such values as equality, happiness, security, or safety. There is a view that public interest, also sometimes held to be equivalent to the 'public good', is roughly synonymous with a definition of 'general welfare', and juxtaposed with autonomy and <i>individual</i> interests.
Receptor	A large molecule on a cell's surface that is a specific target for particular chemicals. In the brain, this is most often neurotransmitters, but it can also include hormones and other endogenous chemicals, that bind to it and signal what is going on outside the cell (signal transduction)
Reinforcement	A neural process within the reward pathway that ensures that an activity or event is seen as <i>salient</i> and motivating. A stimulus that produces this effect within the reward pathway is said to be a <i>reinforcer</i> . Addictive drugs are potent reinforcers.
Reinforcers	Any event or stimulus that motivates an individual to repeat its use or occurrence.
Reinstatement	The resumption of addictive behaviours (e.g. <i>self-administration</i> , <i>conditioned place preference</i> , <i>behavioural sensitisation</i> ) following their extinction. Reinstatement is believed to be an animal model of relapse-like behaviour.
Relapse	The resumption of regular drug use after a period of abstinence, often in response to drug-related cues or stress. Relapse is common after



	addicts have achieved abstinence.
Relapse Prevention	The use of a prophylaxis, usually pharmacological (e.g. naltrexone) or psychological support, to reduce the likelihood of returning to regular drug use. Most drugs used in relapse prevention work by preventing the drug of addiction from binding to its receptor. Drug vaccines have also been developed to reduce relapse to the use of some drugs of addiction (e.g. nicotine, cocaine).
Reuptake	The chemical process whereby signalling molecules or neurotransmitters are removed from the synapse by <i>transporters</i> on the cell surface. Reuptake is an important process that regulates the activity of signalling molecules.
Reward	The neural process that reinforces behaviour and signals that some experience, such as using drugs, is positive. It is usually associated with pleasure or euphoria. It is partly mediated by the release of dopamine into the <i>nucleus accumbens</i> .
Reward Pathway	A central circuit in the brain that reinforces behaviour when activated. Most drugs which activate this reward pathway are addictive, and their effects are usually experienced as rewarding and pleasurable. The circuit includes neurons of the <i>ventral tegmental area</i> , <i>nucleus accumbens</i> , and part of the <i>prefrontal cortex</i> , referred to as the <i>mesolimbic pathway</i> , and the <i>amygdala</i> and <i>hippocampus</i> .
Rights (moral)	Justified (strong) claims to the protection of persons' important interests. When these rights are effective, this protection is provided as something that is owed to persons for their own sakes. Not to be confused with contractual (weak) rights created by agreement, law and <i>conventio</i> (called liberties, powers and immunities).
Salience	The motivating quality of an event or experience. In contrast to <i>reward</i> , salient events need not be pleasurable. They are things that grab our attention, and motivate us to pursue them. Salient events are also reinforcing.
Self-administration	The most widely used animal model of addiction. Animals are trained to perform some behaviour (usually pressing a lever) in order to receive an addictive drug. Animals quickly learn to self-administer most drugs of abuse.
Snus	An oral form of tobacco that has been treated to remove the major carcinogens from traditional chewed tobacco.

Stimuli	Events or experiences that trigger a neurochemical response in the brain.
Striatum	A region deep within the brain that is involved in the planning and regulation of movement and executive control pathways.
Substitute	Any drug that mimics that primary effects of a drug of addiction, that is given to replace the abuse of the addicted drug.
Substitution Treatment	See <i>Maintenance therapy</i> .
Suboxone	A combination of drugs used in the treatment of opioid dependence. Its principal ingredient is <i>buprenorphine</i> but it also contains the opioid antagonist, <i>naloxone</i> , to discourage patients from dissolving and injecting the drug as injecting naloxone produces opioid withdrawal symptoms.
Swiss Heroin Trials	A series of clinical trials of the prescription of injectable pharmaceutical heroin to long-term, treatment refractory heroin addicts. See <i>Heroin prescription trials</i> .
Synaptic Plasticity	Molecular and cellular changes between two cells that either strengthen or weaken their connection. Also see <i>long-term potentiation</i> and <i>long-term depression</i> .
Synapse	The specialised junction between two neurons across which neurotransmitter release allows signalling from one neuron (the presynaptic neuron) to the next (the postsynaptic neuron). Molecular and cellular specialisations at the synapse allow for quick and highly regulated communication between the two neurons.
Tapered Withdrawal	The slowly decreasing administration of an addictive drug, or its agonist, over a period of days or weeks to assist addicted individuals withdraw from their target drug and become abstinent.
Thalamus	The thalamus is the key relay station for all incoming sensory information. It is located deep within the brain, and is responsible for isolating important messages from the mass of sensory information entering the brain.
Tolerance	A physiological state in which an individual is less responsive to the effect of a drug, leading to the use of higher doses. Tolerance is the result of neurochemical changes within the brain as a result of regular drug use. It often leads to <i>physical dependence</i> .
Transporter	A large molecule in the cell membrane that pumps signalling molecules

such as neurotransmitters out of the synapse, thereby regulating their activity.

Ultra-rapid Opioid Detoxification	A form of opioid detoxification that reduces the withdrawal process to 24 hours by administering high doses of the antagonist, naltrexone, while the patient is under general anaesthesia.
Ventral Tegmental Area (VTA)	A group of dopaminergic neurons that make up a key part of the brain's reward pathway. Neurons in the VTA synapse on to neurons in the <i>nucleus accumbens</i> and the <i>prefrontal cortex</i> .
Withdrawal	Symptoms that develop when an individual abruptly stops or abstains from chronic drug use. The symptoms of withdrawal can include nausea, headaches and seizures, depending on the drug of addiction. Some drugs have very mild or no withdrawal symptoms (e.g. cocaine), while others cause intense discomfort (e.g. alcohol, heroin).

# Appendix 1: Taxonomy of Australian Addiction Neuroscience Research Groups

Note: The code listed refers to a tag used to identify researchers as being located at a particular research group in the Endnote database (see the 'caption' field).

## ***Animal Studies***

*School of Biomedical Sciences, University of Newcastle, NSW*  
(Code: SBS, Newcastle)  
Christopher Dayas

*Psychopharmacology lab, School of Psychology, University of Sydney, NSW*  
(Code: Psychopharmacology, Sydney)  
Iain McGregor  
Paul Callaghan  
Lenora Long

*Pain Management Research Institute, University of Sydney, NSW*  
(Code: PMRI, Sydney)  
Mac Christie  
Elena Bagley  
Peregrine Osborne  
Jennifer Hacker

*Department of Pharmacology, University of Sydney, NSW*  
(Code: Pharmacology, Sydney)  
Jonathon Arnold  
Glen Hunt

*Behavioural Neuroscience Laboratory, University of NSW, NSW*  
(Code: BNL, NSW)  
Gavan McNally  
Adam Hamlin  
Kelly Clemens

*Neuropharmacology Lab, Department of Psychology, Macquarie University, NSW*  
(Code: Neuropharmacology, Macquarie)  
Jennifer Cornish

*Drug Dependency, Discipline of Pharmacology, University of Adelaide, SA*  
(Code: Pharmacology, SA)  
Rod Irvine (also does cognitive neuroscience research)  
Adballah Salem

*Addiction Neuroscience Laboratory, Howard Florey Institute, VIC*  
(Code: ANL, HFI)  
Andrew Lawrence  
Michael Cowen

*Pharmaceutical Biology, Victorian College of Pharmacy, VIC*  
(Code: *Pharmaceutical biol, VCP*)  
Ian Coupar  
Dan Malone  
Jennifer Short

### **Cognitive Neuroscience**

*Centre for Mental Health Research, Australian National University, ACT*  
(Code: *CMHR, ANU*)  
Kaarin Anstey  
Tim Windsor  
Bryan Rodgers  
Amanda George

*School of Psychology, Australian National University, ACT*  
(Code: *Psychology, ANU*)  
John Brown

*Centre for Brain and Mental Health Research, University of Newcastle, NSW*  
(Code: *CBMHR*)  
Martin Cohen  
Vaughan Carr  
Amanda Baker

*School of Psychology, University of Wollongong, NSW*  
(Code: *Psychology, Wollongong*)  
Nadia Solowij

*Menzies School of Health Research, NT*  
(Code: *Menzies, NT*)  
Sheree Cairney  
Alan Clough

*Department of Psychiatry, University of QLD, QLD*  
(Code: *Psychiatry, UQ*)  
John Saunders  
Mark Daghish  
David Kavanagh (now at QUT)  
Jason Connor

*Queensland Brain Institute, University of QLD, QLD*  
(Code: *QBI, UQ*)  
Rob Hester

*School of Psychology, University of QLD, QLD*  
(Code: *Psychology, UQ*)  
Natalie Loxton

*School of Psychology, Griffith University, QLD*  
(Code: *Psychology, GU*)  
Sharon Dawe

*Orygen and Melbourne Neuropsychiatry Centre, University of Melbourne, VIC*  
(Code: Uni of Melb)  
Dan Lubman  
Murat Yucel

*School of Psychology, Psychiatry and Psychological Medicine, Monash University, VIC*  
(Code: Psychology, Monash)  
Julie Stout

*Drug Dependence, Pharmacology, University of Adelaide, SA*  
(Code: Pharmacology, SA)  
Jason White  
Olga Lopatko

*Unit for Education and Research in Alcohol and Drugs, University of WA, WA*  
(Coded: ERAD, Uni of WA)  
Gary Hulse

*Pharmacology and Toxicology, University of WA, WA*  
(Coded: Pharm and Toxic, Uni of WA)  
Kyle Dyer  
Mathew Martin-Iverson

### **Human Neuropathology**

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## Appendix 2: Australian Addiction Neuroscience

### Publications

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## Appendix 3: Bibliography of Addiction Neurobiology Research

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