Alcohol and psycho-active substance misuse has far-reaching social, psychological and physical consequences. Advances in neuroimaging technology have allowed neurobiological theories of addiction to become better characterized. We describe the neurobiology of dependence, withdrawal, abstinence and craving states in alcohol, stimulant and opiate misuse. Structural neuroimaging techniques such as CT and MRI with new analytical approaches such as voxel-based morphometry have shown wide-spread changes in stimulant and opiate abuse and atrophy, particularly in the frontal lobes, in alcoholism. Functional neuroimaging techniques such as PET, SPECT and fMRI reveal altered regional cerebral activity by all drugs of abuse. The neurochemistry of addiction, particularly involving dopamine, serotonin, opiate and GABA, has been studied with PET and SPECT and similarities between all drugs of abuse have been found such as reduced dopaminergic markers. The evidence derived from these advances in neuroimaging is likely to herald the emergence of new biological treatments in this important field.

The profound social, psychological, physical and economic consequences of misuse of alcohol and other psycho-active substances have been well documented. About a quarter of men and one in seven women in the UK drink more than recommended limits\(^1\). About 500,000 people in the UK fulfil criteria for opiate addiction, with its associated high morbidity and mortality, and use of cocaine is rising, currently accounting for 10% of reported illicit drug use\(^1\). While psychological theories appear to predominate in clinical practice and form the basis for most existing treatments, as neurobiological theories become more fully defined and evidence-based, their impact on treatment is likely to increase. This review is not exhaustive, but illustrates how neuroimaging is playing a critical role in this process for some drugs of abuse. With neuroimaging, the neurobiology of addiction through its different stages of intoxication, dependence, withdrawal, and abstinence can now be directly measured \textit{in vivo}.
Alcohol

Structural neuroimaging

Every clinician is aware that alcohol damages the brain, causing atrophy, and early CT studies confirmed this showing increased ventricular and intrasulcal volumes in alcoholics. Magnetic resonance imaging (MRI) has provided better discrimination between grey and white matter and CSF, and more precise quantification of structural changes. Reduced volume in the frontal and temporal cortices, hippocampus, mammillary bodies and cerebellum have been reported, with greater loss seen in older age groups. Reduced white matter in the temporal lobes has been related to a history of seizures, but it is not clear whether it is a cause or a consequence.

MRI has also been valuable in examining changes in gross brain volume over time. For instance, Pfefferbaum et al. showed an increase in anterior cortical grey matter volume with reduced CSF volume in the first month of abstinence. These changes were initially attributed to ‘rehydration’ but later to sprouting of new dendrites and axons. MRI and proton MR spectroscopy (MRS) have provided clinicians with evidence that neuronal regeneration (as evidenced by increased N-acetylaspartate/choline) is an important factor underlying the reversal of atrophy. Awareness of this can be useful in enhancing motivation for change in alcohol dependence.

Wernicke’s encephalopathy and Korsakoff’s syndrome are, respectively, acute and chronic clinical syndromes associated with thiamine deficiency seen in alcohol dependence. MRI studies in alcohol-dependent patients with these clinical features have identified widespread reductions in grey-matter volumes especially in the thalamus, diencephalic regions and median and dorsal raphe nuclei. Neuropathologists have long regarded mammillary body shrinkage as a cardinal feature in patients with Korsakoff’s syndrome; however, MRI has provided evidence to challenge this theory. Significant shrinkage was detected in some non-amnesic alcoholics, but was universal in patients with Korsakoff’s syndrome, suggesting a continuum of mammillary body pathology in chronic alcoholism.

Classically, post-mortem work described greater vulnerability of white than grey matter to alcohol. A recent advance, diffusion tensor imaging (DTI), allows quantification of the integrity of cerebral white matter and damage has been reported within all brain regions, particularly in the genu and centrum semiovale, in alcoholics.

Functional neuroimaging

Cerebral blood flow, perfusion and metabolism

As might be expected, PET and SPECT neuroimaging studies have shown reduced blood flow, perfusion or metabolism in alcohol...
dependence, with the frontal lobe being particularly susceptible\(^9\). Improvement in cerebral activity is seen during early abstinence. Volkow et al\(^{10}\) reported increased metabolism, particularly in frontal regions and more recently frontal lobe rCBF was found to increase progressively with abstinence and return to premorbid levels within 4 years\(^{11}\). Notably, George et al\(^{12}\) showed that multiple detoxifications were associated with greater levels of hypoperfusion. This emphasises the need to optimise the treatment programme to encourage abstinence rather than repeated detoxifications.

Neuropsychological impairments, which in general initially involve the frontal lobe, and ultimately alcoholic dementia are functional consequences of these changes. Although not every study has shown such a relationship, cerebral deficits identified through neuroimaging have been associated with neuropsychological impairment\(^9\). Clinically, whilst appearing neurologically and psychiatrically healthy, many alcoholics may have subtle deficits detectable only by targeted neuropsychiatric assessment that could impact on treatment. A recent study in a healthy population of alcoholics found reduced medio-frontal lobe metabolism correlated with impairments in verbal fluency\(^{13}\).

**Neurochemistry**

Neuroimaging has focused on the GABA, dopamine and serotonin systems since they are involved in the neurobiology of alcoholism and its treatment\(^{14,15}\).

The GABA-benzodiazepine receptor complex (GBzR) has been an intense focus of interest since many of alcohol’s central effects are mediated through its agonist action at the GBzR and benzodiazepines alleviate alcohol withdrawal symptoms\(^{14}\). It has been proposed that reduced GABA-ergic function is associated with vulnerability to alcoholism. Reduced levels of the GBzRs, particularly in the frontal lobes, have been reported in imaging studies of alcohol dependence using \([^{11}C]\)-flumazenil PET\(^{16}\) or \([^{123}I]\)-iomazenil SPECT\(^{17,18}\). One study excluded grey matter atrophy as a significant contributor to this reduction\(^{18}\). It is not known whether the reduced levels of GBzRs preceded alcohol abuse. These findings may reflect an alteration in the subunit profile of the GBzR that is seen in animal models as a means of reducing sensitivity to alcohol (i.e. tolerance).

Serotonin is implicated in many disorders such as anxiety and depression that co-exist with alcoholism and also in controlling impulsive behaviour\(^{14}\). Using \([^{123}I]\)-\(\beta\)-CIT SPECT, Heinz et al\(^9\) reported that alcohol dependence was associated with reduced levels of the 5-HT transporter in the raphe nucleus in the brainstem (the only region which could be imaged); the reduction correlated with ratings of depression and anxiety. Notably this reduction, but not alcoholism, was associated
with a particular allelic variation (Il) of the 5-HT transporter, suggesting that this polymorphism mediates susceptibility to neurotoxicity.\textsuperscript{20}

Dopamine is a key neurotransmitter in addiction. All drugs of abuse (except benzodiazepines) increase dopaminergic function in the mesolimbic system, the critical pathway in mediating reward. More recently, a role in associative learning has been recognised and evidence has emerged that a hypodopaminergic state occurs in withdrawal.

Although Volkow\textsuperscript{21} reported no differences in striatal dopamine transporter (DAT) levels compared with controls, subsequent studies have reported reductions although only in a subtype of alcoholism. SPECT with another tracer was used to quantify striatal DAT levels in violent (akin to type 2 alcoholism, characterised by early age of onset, antisocial personality traits) and non-violent (akin to type 1, characterised by late age of onset and anxiety) alcoholics. Compared with controls, reduced DAT levels were seen in the non-violent group and slightly higher levels in violent group.\textsuperscript{2} This has partly been replicated by Repo\textit{et al.}\textsuperscript{23} who described reduced DAT levels in type 1 alcoholism. These studies suggest that subtypes have a particular neurobiology that may have implications for treatment.

Clinically, withdrawal and early abstinence is a turbulent time and not surprisingly changes in neurochemistry have been found. Laine\textsuperscript{24} studied alcoholics in early withdrawal and found that DAT levels were significantly lower than in controls with recovery to normal levels, often in the first 4 days. This supports the hypothesis that hypodopaminergic function occurs in withdrawal as does a study by Guardia\textit{et al.}\textsuperscript{25} which found that increased dopamine D2 receptor (DRD2) availability, secondary to low dopamine levels, were associated with greater risk of relapse.

Volkow\textit{et al.}\textsuperscript{21}, by contrast, reported reduced striatal DRD2 levels in alcohol dependence. Until the recent development of a very high affinity tracer, \textsuperscript{123}I-epidepride, DRD2 could only be imaged in the striatum due to the low levels elsewhere in the brain. D2/D3 receptors can now be measured in the temporal lobe and, using this tracer, Repo\textit{et al.}\textsuperscript{23} found no differences in receptor levels here in type 1 alcoholism.

\textbf{Craving}

Craving is a term often used by dependent people to describe their difficulty in controlling their drug use and is implicated in relapse, but it has proved difficult to define this term rigorously in a scientific context. Craving is a multidimensional phenomenon incorporating a desire to gain a positive feeling (\textit{e.g.} euphoria), to overcome a negative feeling (\textit{e.g.} withdrawal) or an ‘urge to use’. Cue-exposure paradigms are widely used to study ‘craving’ and have recently been combined with
neuroimaging to help characterize the neural networks associated with this experience.

There are only a few neuroimaging studies describing neural activation with craving for alcohol with inconsistent results, likely due to different paradigms. Modell and Mountz\textsuperscript{26} described increased activity in the right head of caudate nucleus with [$^{99m}$Tc]-HMPAO SPECT. Two recent functional MRI (fMRI) studies have found craving associated with activation in the left prefrontal cortex and anterior thalamus in non-treatment seeking alcoholics\textsuperscript{27} and in the right amygdala and hippocampal area as well as in the cerebellum\textsuperscript{28}. These regions are part of the limbic system and, therefore, activation here is not surprising with craving.

**Stimulants**

There have been many functional imaging studies investigating the effects of stimulants on the brain. The continuing rise in the use of stimulants, for example cocaine and methamphetamine, is causing increasing public health concerns. Stimulant use, especially that of crack cocaine, usually follows a relapsing course driven by powerful cravings for further use, emerging almost the instant the extreme euphoria of the drug has worn off.

**Structural studies**

There are limited studies on the structural changes in stimulant abusers, but generally changes consistent with infarcts and haemorrhages are seen. Recently, striatal hypertrophy has been reported in cocaine addicts that is thought to be secondary to the depletion of dopamine and hypoperfusion\textsuperscript{29}. Voxel-based morphometry has been developed to measure the concentration, rather than volume, of white and grey matter from MRI. Using this technique, reduced levels of grey matter in several regions including the orbitofrontal (OFC), cingulate and temporal cortices of cocaine addicts has been reported\textsuperscript{30}. Diffusion tensor imaging has recently shown disrupted OFC connectivity\textsuperscript{31}.

**Functional neuroimaging**

**Cerebral blood flow, perfusion and metabolism**

Cocaine addiction is associated with wide-spread reductions in metabolism and perfusion that persist in abstinence\textsuperscript{32–34}. This is likely to be due to the vasoconstrictive effects of cocaine which result in cerebral
infarcts. A similar pattern is seen with amphetamine abuse\textsuperscript{35,36}. Methamphetamine abuse is also associated with reduced cerebral activity, particular in the striatum, together with hypermetabolism in parietal cortex, which is thought to reflect gliosis/inflammation\textsuperscript{37,38}.

As with alcoholism, increased metabolism during the early withdrawal period from cocaine has been reported in the OFC followed by hypometabolism. It was suggested that the increase is associated with craving (see below) which is high during this period. This group postulated that activity in the OFC is indicative of the involvement of neural circuits associated with repetitive or compulsive behaviours rather than merely pleasure and reward\textsuperscript{33}. More recently, Volkow \textit{et al}\textsuperscript{39} hypothesised that reduced activity in the OFC was as a result of reduced dopaminergic input since activity here correlated with striatal DRD2 levels. Increasing dopaminergic activity with methylphenidate did not increase metabolism in the OFC of all cocaine addicts, but in those that it was, craving was experienced. This study suggests that increasing dopaminergic function is not sufficient to redress damage from cocaine and that the OFC is critical to craving.

fMRI has been used to examine the effects of drug abuse on cognitive processes thought to be impaired by, or involved in, drug abuse. In an fMRI study, Paulus \textit{et al}.\textsuperscript{40} found that methamphetamine dependence was associated with reduced activation in the prefrontal cortex reflected as impaired decision-making, and that activation in the OFC predicted the duration of methamphetamine abuse.

**Neurochemistry**

As described, the dopaminergic system is critical in addiction, and drugs such as cocaine and amphetamine act directly on this system to increase dopamine resulting in pleasure. There are several studies \textit{in vivo} in man to support this premise. Volkow\textsuperscript{41} reported that blockade of the DAT by cocaine positively correlated with experiencing a ‘high’. At least 50\% occupancy of DAT was required for a ‘high’.

More recently, \textit{in vivo} endogenous dopamine levels can be assessed in man using [\textsuperscript{11}C]-raclopride PET since this dopaminergic D2 receptor marker is sensitive to dopamine. Schlæpfer \textit{et al}\textsuperscript{42} used this protocol to show that cocaine increased dopamine levels in the striatum that were related to its peak physiological and subjective effects. Similarly, Laruelle \textit{et al}\textsuperscript{43} using [\textsuperscript{123}I]-IBZM SPECT reported that amphetamine increased dopamine levels and this correlated with subjective euphoria, alertness and restlessness. Therefore, it is clear that in man dopamine is key in mediating many of the effects of stimulants which supports the fact that the dopaminergic system has been a key target for pharmacotherapy, albeit without much success to date.

Methylphenidate is used clinically to treat attention deficit disorder and concerns have been expressed about giving a drug with abuse
potential to children already at higher risk of substance misuse. Compared to other stimulants, methylphenidate abuse is minimal and Volkow et al\textsuperscript{44} have shown that its pharmacokinetics contribute to this. The faster the rate of onset of a drug, the higher its addictive potential. The rate of onset of i.v. cocaine and i.v. methylphenidate to the DAT is similar, but that of oral methylphenidate is much slower. Whether methylphenidate is given i.v. or orally, its off-rate from the DAT is much slower than that for cocaine. Both enter the brain equally fast although cocaine is cleared more quickly. DAT is less available with methylphenidate and becomes saturated with repeated use resulting in no further increases in dopamine, thus lowering its abuse potential.

Chronic exposure to cocaine results in decreased DRD2 receptors, which persist for 3–4 months\textsuperscript{35}. As described above, this reduction correlates with reduced metabolism in the OFC which receives projections from the nucleus accumbens in the ventral striatum\textsuperscript{33}. In addition, dopaminergic function is reduced in cocaine addicts. The amount of dopamine released by methylphenidate in cocaine addicts was 50\% less than that in the controls, and the ‘high’ was perceived as less intense. This blunted dopaminergic response in cocaine addicts may lead to increased drug use in an attempt to compensate for the decreased stimulation in this dopaminergic reward pathway.

The activity of the dopamine system has recently been shown to influence experiencing pleasure from drugs. Through a series of experiments in healthy controls with methylphenidate, Volkow et al\textsuperscript{46} showed that low DRD2 levels were associated with pleasure and those with high DRD2 levels found methylphenidate unpleasant. Therefore, activity in the dopaminergic system, not surprisingly, appears to be involved in the vulnerability to addiction.

Similarly, reduced levels of striatal dopamine D2 receptor have been reported in methamphetamine addicts which correlated with reduced metabolism in the OFC. Striatal DAT levels are reduced in methamphetamine users and this is associated with motor and memory impairment\textsuperscript{47,48}. Sekine et al\textsuperscript{49} demonstrated striatal DAT levels were inversely correlated with severity of psychiatric symptoms and duration of use of methamphetamine, but not abstinence, suggesting long-lasting damage.

**Craving**

Identification of brain areas activated during craving for stimulants have generated considerable interest and neuroimaging studies have produced remarkably consistent results. Grant et al\textsuperscript{56} using [\textsuperscript{18}F]-FDG PET first showed that craving for cocaine correlated with increased activity in the
amygdala and dorsolateral prefrontal cortex. Childress et al\textsuperscript{51} similarly showed that cocaine craving was associated with increased activity in the amygdala, but also in the anterior cingulate cortex. These regions have all been implicated in addiction with the amygdala involved in associative learning (\textit{i.e.} between cue and drug), the anterior cingulate cortex with emotional processing and the dorsolateral prefrontal cortex with memory.

More recently, fMRI studies have shown activation in similar areas including the anterior cingulate, prefrontal and orbitofrontal cortices in response to salient cues\textsuperscript{52,53}. The increased temporal resolution of fMRI was exploited by Wexler et al who showed that the anterior cingulate cortex was activated in cocaine addicts even if they did not go on to experience craving for cocaine (see opiate craving below). The temporal and spatial resolution of fMRI has also been used by Breiter et al\textsuperscript{54} to map the distinct regional effects of i.v. cocaine in the brain and relate these to subjective effects. ‘Rush’ was associated with activation in areas including the basal forebrain, caudate, cingulate and prefrontal cortices, whereas activation associated with craving occurred in the nucleus accumbens, right parahippocampal gyrus and prefrontal cortex.

**Ecstasy**

In the UK, 3,4-methylenedioxymethamphetamine (MDMA) or ‘Ecstasy’ receives much attention. It is increasingly popular amongst young people despite evidence of toxicity to serotonergic neurons in animals and fears of ensuing psychiatric morbidity in man.

Reduced 5-HT transporters (5-HTT) have been reported in a number of studies suggesting serotonergic damage from Ecstasy use. Two early studies with \([^{11}\text{C}]-\text{McN}-5652\) PET and \([^{123}\text{I}]-\beta\)-CIT SPECT showed reduced 5-HTT throughout the brain in Ecstasy users\textsuperscript{55,56}, but methodological concerns have been expressed. More recently, Reneman et al\textsuperscript{57} using \([^{123}\text{I}]-\beta\)-CIT SPECT showed reduced 5-HTT levels in cortical regions in Ecstasy users but not in ex-Ecstasy users. Although verbal memory was impaired, no correlation was seen between performance and 5-HTT levels. Further studies are required to characterize serotonergic changes with Ecstasy use in man and to take into account confounders such as other drug use and psychiatric morbidity.

**Opiates**

In the UK, opiate dependence is associated with higher rates of morbidity than all other illicit drugs and accounts for the largest
proportion of people in treatment services. There are only a few neuroimaging studies investigating the consequences of opiate misuse and addiction on the brain.

**Structural imaging**

There is little evidence from CT or MRI of consistent structural changes associated with long-term opiate use\(^{58}\).

**Functional neuroimaging**

**Imaging the acute effects of opiates**

Two studies have examined the effect on the brain of an acute dose of opiates. Firestone et al\(^ {59}\) used \(^{15}\)O–H\(_2\)O PET to measure rCBF in response to an acute dose of the short-acting opiate agonist, fentanyl. There was significantly increased activity in cingulate, orbitofrontal and medial prefrontal cortices, as well as the caudate nuclei. These areas are involved in learning, reward, and addiction. Schlaepfer et al\(^ {60}\) similarly used \(^{99m}\)Tc-HMPAO SPECT to compare the effects of hydromorphone, an agonist at the mu receptor, which is responsible for the pleasurable effects of opiates, to those of butorphanol, an agonist at the kappa receptor, which mediates dysphoria. Hydromorphone, but not butorphanol, induced more euphoric effects and produced significant increases in activity in the anterior cingulate cortex, amygdalae, and thalamus. These regions are part of the limbic system, which is key in addiction.

**Effects of substitution pharmacotherapy and chronic opioid use in opiate addicts**

Clinically, methadone, a mu agonist, is the most widely used substitution therapy for opiate addicts and greater efficacy is seen at higher doses (60 mg) of methadone. It is presumed that higher doses of methadone occupy more opiate receptors, thus preventing access to the receptor of any opiate used ‘on top’, but this has not been shown in man. Kling et al\(^ {61}\) imaged opiate receptors of patients maintained on methadone with \(^{18}\)F-cyclofoxy, an antagonist at the mu and kappa opioid receptors. They found that methadone resulted in fewer available opioid receptors, particularly in thalamus, amygdala, caudate, anterior cingulate cortex, and putamen, compared with normal controls. A correlation between opiate receptor availability and plasma methadone levels was only seen in the caudate and putamen.

Buprenorphine is increasingly used in substitute therapy and is a partial agonist at the mu receptor and antagonist at the kappa receptor;
it has several advantages over methadone including reduced risk of respiratory depression and dysphoria. Zubieta et al. used the mu selective PET radioligand \([^{11}C]\)-carfentanyl to measure opiate receptor availability in three patients maintained on differing doses. There was dose-dependent inverse relationship between buprenorphine dose and opiate receptor availability with 36–50% occupancy at 2 mg and 79–95% at 16 mg.

Chronic opiate agonist treatment in animal models has been shown to increase opiate receptor levels, albeit inconsistently. Preliminary data from our group and the study of Zubieta et al. also suggest an increase in man. A trend towards a small increase in opiate receptor levels was found in opiate addicts immediately after detoxification from methadone and in subjects maintained on buprenorphine, opiate receptor availability was increased compared to controls.

**Opiate withdrawal**

The opiate antagonist, naloxone, has been used to precipitate withdrawal by Wang et al. \([^{11}C]\)-Raclopride PET was used to characterise dopaminergic function in withdrawal, which was hypothesized from animal models to be reduced. Whilst a significant decrease in dopamine DRD2 receptor levels was found in opiate-dependent subjects compared with controls, there was no significant change in striatal dopamine concentration during withdrawal. It is, therefore, not clear whether altered dopaminergic levels do play a role in opiate withdrawal.

**Craving**

There have only been a few studies on opiate craving, but there are similarities in the regions activated to those seen for cocaine, supporting the hypothesis that there is a common pathway involved in addiction for drugs of abuse. Daglish et al. used a \([^{15}O]\)-H\(_2\)O PET individualised cue-exposure paradigm and reported increased rCBF in the anterior cingulate cortex was seen in response to the salient drug cue, whereas craving itself was associated with activation in the left orbitofrontal cortex. This is similar to the findings of Wexler et al. on cocaine. Sell et al. used similar techniques to show ‘urge to use’ correlated strongly with increase rCBF in the inferior frontal and orbitofrontal cortices. Therefore, the orbitofrontal cortex appears to be associated with craving and further studies are required to explore the contributions of other regions to the experience of craving.

**Conclusions**

Neuroimaging is playing a central role in determining the neurobiology of addiction. Reductions in dopamine D2 receptors have been reported
for all drugs of abuse studied including cocaine, methamphetamine, alcohol and opiates suggesting that these reductions are not specific to any type of addiction, but reflect a common abnormality in addiction. In addition neural networks involved in craving for different drugs of abuse appear similar. With greater sophistication of imaging techniques, there will be further exploration of these craving circuits and better understanding of the neurobiology of addiction.

References

3 Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. Arch Gen Psychiatry 1998; 55: 905–12
12 George MS, Teneback CC, Malcolm RJ et al. Multiple previous alcohol detoxifications are associated with decreased medial temporal and paralimbic function in the postwithdrawal period. Alcohol Clin Exp Res 1999; 23: 1077–84
27 George MS, Anton RF, Bloomer C et al. Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Arch Gen Psychiatry* 2001; 58: 345–52
30 Franklin TR, Acton PD, Maldjian JA et al. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry* 2002; 51: 134–42
31 Lim KO, Choi SJ, Pomara N, Wolkin A, Rotrosen JP. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. *Biol Psychiatry* 2002; 51: 890–5
57 Reneman L, Booij J, de Bruin K et al. Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet* 2001; 358: 1864–9
58 Nutt DJ, Daglish MR. Structural and functional neuroimaging of the effects of opioids. In:


