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REVIEW

What have positron emission tomography and 'Zippy' told us about the neuropharmacology of drug addiction?

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Translational molecular imaging with positron emission tomography (PET) and allied technologies offer unrivalled applications in the discovery of biomarkers and aetiological mechanisms relevant to human disease. Foremost among clinical PET findings during the past two decades of addiction research is the seminal discovery of reduced dopamine $D_{2/3}$ receptor expression in the striatum of drug addicts, which could indicate a predisposing factor and/or compensatory reaction to the chronic abuse of stimulant drugs. In parallel, recent years have witnessed significant improvements in the performance of small animal tomographs (microPET) and a refinement of animal models of addiction based on clinically relevant diagnostic criteria. This review surveys the utility of PET in the elucidation of neuropharmacological mechanisms underlying drug addiction. It considers the consequences of chronic drug exposure on regional brain metabolism and neurotransmitter function and identifies those areas where further research is needed, especially concerning the implementation of PET tracers targeting neurotransmitter systems other than dopamine, which increasingly have been implicated in the pathophysiology of drug addiction. In addition, this review considers the causal effects of behavioural traits such as impulsivity and novelty/sensation-seeking on the emergence of compulsive drug-taking. Previous research indicates that spontaneously high-impulsive rats – as exemplified by 'Zippy' – are pre-disposed to escalate intravenous cocaine self-administration, and subsequently to develop compulsive drug taking tendencies that endure despite concurrent adverse consequences of such behaviour, just as in human addiction. The discovery using microPET of pre-existing differences in dopamine $D_{2/3}$ receptor expression in the striatum of high-impulsive rats suggests a neural endophenotype that may likewise pre-dispose to stimulant addiction in humans.

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Abbreviations

5-CSRTT, five choice serial reaction time task; 5-HT, 5-hydroxytryptamine; ADHD, attention deficit hyperactivity disorder; *BP*, binding potential; CBF, cerebral blood flow; CIT, 2β-carboxymethoxy-3β-(4-iodophenyl)tropane; DASB, *N*,*N*-dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine; DAT, dopamine transporter site; DMFP, desmethoxyfallypride; DSM, Diagnostic and Statistical Manual; FDG, fluorodeoxyglucose; FDOPA, fluoro-L-dihydroxyphenylalanine; FLB 457, *N*-(1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide; HMPAO, hexamethylpropylene amine oxime; HPLC, high performance liquid chromatography; IBZM, iodobenzamide; ICSS, intra-cranial self-stimulation; IPT, N-(3-iodopropen-2-yl)-2beta-carbo-methoxy-3beta- (4-chlorophenyl)tropane;

MAO, monoamine oxidase; NAcb, nucleus accumbens; NET, noradrenaline reuptake inhibitor; NMSP, 3-*N*-methylspiperone; OFC, Orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; SERT, serotonin transporter site; SPECT, single photon emission computer tomography; TAC, time–activity curve; TRODAT, [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]methyl](2-mercaptoethyl)amino]ethyl]amino] ethanethiolato(3-)-*N2,N2′,S2,S2′*]oxo-[1*R*-(*exo-exo*)]; VOI, volume of interest; VTA, ventral tegmental area

Introduction

Misuse of addictive substances including psychostimulant drugs and alcohol is a major and growing cause of morbidity and mortality in the United Kingdom (Godfrey and Cave, 2005). Despite extensive research, the aetiology of drug addiction remains remarkably poorly understood in neural terms, even though a detailed knowledge has been obtained of the primary molecular sites in the brain that mediate the reinforcing effects of widely abused drugs such as cocaine and heroin (Nestler *et al.*, 1993; Wise, 1996; Kalivas and Volkow, 2005). The influential discovery by Olds and Milner of intracranial self-stimulation (ICSS) marked a major turning point for research on the neuropharmacology of addiction (Olds and Milner, 1954). The subsequent discovery of brain dopamine led to the Nobel Prize in Medicine awarded in the year 2000 to Professors Carlsson, Greengard and Kandel. In the intervening years, it was established that dopaminergic fibres arising in the ventral tegmental area (VTA) of the mesencephalon and projecting to limbic cortico-striatal structures [nucleus accumbens (NAcb), olfactory tubercle, amygdala, orbitofrontal cortex (OFC) and prefrontal cortex (PFC)] were effective substrates for ICSS. This linkage of neurochemical anatomy and behaviour fuelled interest in the brain dpoamine systems as neural substrates for the rewarding properties of both natural (e.g. food) and drug incentives. Indeed, the hypothesis that drugs of abuse mediate their hedonic or pleasurable effects through dpoamine release in mesolimbic regions, including especially the NAcb, has dominated addiction research for more than two decades (Di Chiara and Imperato, 1988; Wise, 1996).

Although the dopamine model continues to influence and inform contemporary theories of drug addiction, supplementary mechanisms have been postulated to explain the emergence of *compulsive* drug seeking, a defining hallmark of addiction involving continued drug use in the face of mounting negative consequences of such behaviour (Hyman and Malenka, 2001; Everitt *et al.*, 2008). For example, the development of compulsive drug seeking has been posited to represent a failure in top-down, executive control, brought about by the toxic effects of drugs themselves on PFC/OFC functioning (Jentsch and Taylor, 1999; Volkow *et al.*, 2001; Everitt *et al.*, 2008; Garavan *et al.*, 2008; Kalivas, 2008). More specifically, the progression from first drug use to compulsive drug use has been hypothesized to represent a surrender of control over drug seeking by the PFC and ventral striatum to the dorsal striatum, establishing a dysfunctional gradient of neural abnormalities thought likely to encourage the emergence of drug-seeking habits (Everitt and Robbins, 2005).

Increasing evidence also suggests that drug addiction is linked to certain personality traits (e.g. risk-taking, novelty- and sensation-seeking, impulsiveness), and is over-represented in people diagnosed with certain childhood and adolescent psychiatric disorders, including conduct disorder and attention-deficit hyperactivity disorder (ADHD) (Levin and Kleber, 1995; Adams *et al.*, 2003; Chakroun *et al.*, 2004; Dawe and Loxton, 2004; Verdejo-Garcia *et al.*, 2008). Recent research based on prospective studies in adolescents indicates that clinical impulsivity, i.e. rash or risky behaviour and a strong tendency towards sudden poorly judged decisions and actions (Evenden, 1999), may actually *pre-date* problematic drug use (Nigg *et al.*, 2006; Wong *et al.*, 2006b) and thereby, potentially, contribute causally to drug abuse and addiction (Verdejo-Garcia *et al.*, 2008). Consistent with this view, there is growing evidence for a substantial involvement of genetic variables in complex personality traits related to impulsivity and clinical disorders of impulse control, such as ADHD, which account for a significant proportion of the individual's vulnerability to drug addiction (Uhl, 1999; Kreek *et al.*, 2005). Indeed, twin and family studies yield estimates of inheritability of vulnerability to drug addiction as high as 60% (Kreek *et al.*, 2005). Such influences are hypothesized to have an important bearing on the pathway to drug addiction, including initiation of drug use, severity of drug dependence and risk for relapse (Tsuang *et al.*, 1999; Uhl, 1999).

Impulsivity is a multidimensional behavioural construct encompassing several seemingly distinct classes of behaviour that generally involve a predisposition towards rapid, unplanned or premature actions and which are often risky and result in negative consequences (Evenden, 1999; Moeller *et al.*, 2001). It is often contrasted with compulsivity,

which refers to the maladaptive tendency to persist or perseverate responding, *despite* adverse consequences (Fineberg *et al.*, 2010). In general, brain imaging research involving human drug addicts (with positron emission tomography (PET) and magnetic resonance) is mainly based on impulsive personality traits and cognitive measures of inhibitory response control because, in such settings, compulsive behaviour is difficult to assess in human participants. It is therefore difficult to predict whether volunteers participating in such studies will more likely develop later compulsive drug seeking habits. Research in animals avoids such issues by allowing behavioural and cognitive measures to be precisely assessed prior to drug exposure (Dalley *et al.*, 2005a,b; Briand *et al.*, 2008).

Paradigms used to assess impulsivity can broadly be divided into two categories; those that measure impulsive decision-making and those that measure impulsive action (Winstanley *et al.*, 2006; Dalley *et al.*, 2008; Pattij and Vanderschuren, 2008). Impulsive decision-making is commonly assessed using delay-discounting procedures where subjects must choose between a small, immediate reward and a larger, but delayed reward. Impulsive subjects are intolerant of delayed rewards and consequently opt preferentially for immediate, small magnitude rewards, a deficit also present in rats with selective lesions of the NAcb (Cardinal *et al.*, 2001). Action impulsivity is typically assessed by response inhibition paradigms such as the go/no-go and stop-signal reaction time tasks and, in rodents, by the five choice serial reaction time task (5-CSRTT). Collectively, these tasks require subjects to inhibit a prepotent motor response or to cancel an already initiated response in the case of the stop-signal reaction time task (Winstanley *et al.*, 2006).

A number of studies in laboratory animals support a causal link between behavioural impulsivity and drug addiction. For example, an increase in delay discounting impulsivity predicts the acquisition or *initiation* of cocaine self-administration in rats (Perry *et al.*, 2005). In contrast, the maintenance phase of drug use, which is often accompanied by drug bingeing and *escalation*, is influenced by inter-individual variation in action impulsivity (Dalley *et al.*, 2007; Diergaarde *et al.*, 2008). Specifically, rats selected for spontaneously high levels of impulsivity on the 5-CSRTT, an automated operant procedure to assess sustained visual attention and action impulsivity (Robbins, 2002), subsequently maintain higher rates of intravenous cocaine and nicotine self-administration than low-impulsive rats (Dalley *et al.*, 2007; Diergaarde *et al.*, 2008). Trait-like impulsivity on the 5-CSRTT is exemplified by 'Zippy', an intrinsically impulsive rat that shows an additional impairment in delay discounting (Robinson *et al.*, 2009). The relevance of Zippy and his impulsive counterparts to the aetiology of drug addiction will be discussed later in this review.

This review first summarizes the basic principles of molecular imaging as a tool of psychopharmacology. We next present a comprehensive review and synthesis of PET and SPECT studies that have shed light on the neuropharmacology of drug addiction, noting that this approach is most fully developed for the brain dopamine systems. We also discuss how investigating inter-individual differences in dopamine receptor function can help resolve why some individuals are particularly disposed progressively to lose control over their drug intake and ultimately develop drug-seeking habits. Drug and molecular targets cited in this review conform to published guidelines (Alexander *et al.*, 2009).

Principles of molecular imaging

Molecular imaging with PET and also single photon emission computed tomography (SPECT), an allied technology, has been widely used to investigate the different stages of the addiction cycle from the initial site of drug action to the long-term effects of chronic drug exposure on neurotransmitter function and regional brain activity (Volkow *et al.*, 2003; Buchert *et al.*, 2004; Martinez *et al.*, 2004). In common with other imaging modalities, PET allows repeated assessment in the same subject, a feature that can readily be exploited in animal models of addiction where drug exposure is tightly controlled. PET and SPECT are non-invasive autoradiographic methods for molecular and physiological imaging of the living brain. As such, the visualization of a physiological process or molecular target is achieved through the use of a tracer substance, which incorporates in its structure a suitable radionuclide. In the case of nuclear imaging by SPECT, the metastable nuclear isomer technetium-99m can be generated on-site, and incorporated into the structure of a tracer [e.g. [^{99m}Tc]hexamethylpropylene amine oxime (HMPAO) for studies of cerebral blood flow (CBF)], whereas iodine-123 must first be produced in a cyclotron prior to radiotracer synthesis (e.g. [^{123}I]iodobenzamide (IBZM), for studies of dopamine $D_{2/3}$ receptors). The SPECT radionuclides decay in the course of a day or two, with the release of a single energetic photon or γ-ray, which can be mapped to its source in living brain using SPECT.

The brief physical half-lives for decay of common PET radionuclides dictate that they are generated with a cyclotron near the site of use (fluorine-18; $t_{1/2}$ 109 min) or on-site (carbon-11; $t_{1/2}$ 20 min,

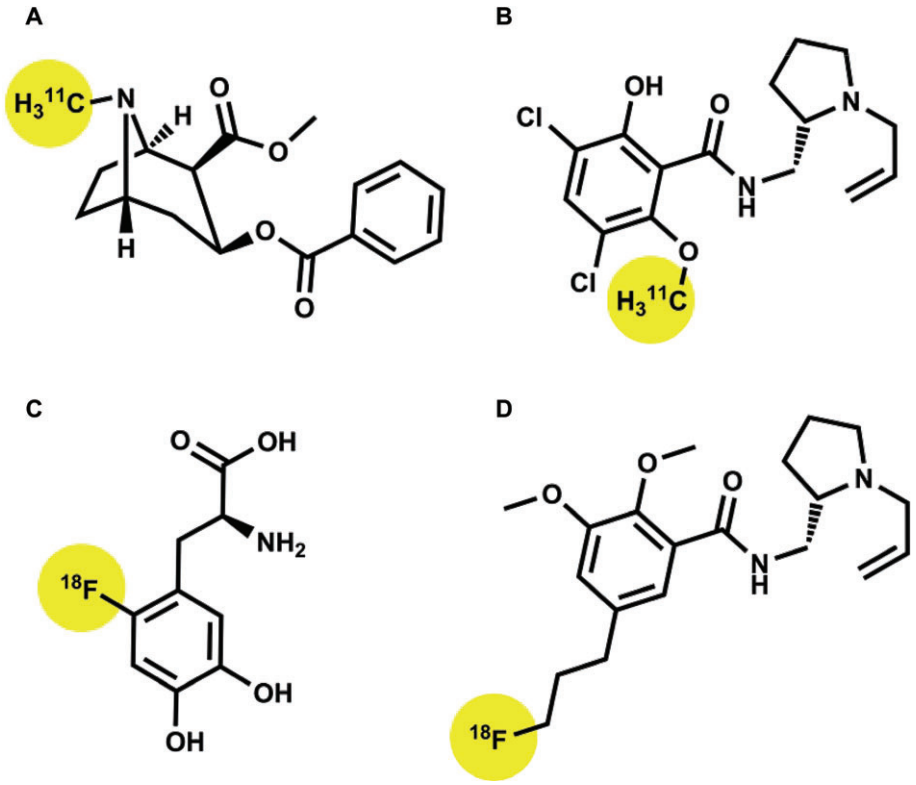

Figure 1

Common PET ligands used to probe dopamine function in drug addiction. Binding sites include dopamine, NA and 5-HT re-uptake transporters (cocaine 'A'), dopamine $D_{2/3}$ receptors (raclopride 'B'; fallypride 'D') and dopamine synthesis (FDOPA 'C'). The molecular positions of carbon-11 and fluorine-18 radioisotopes are highlighted in each case.

oxygen-15, $t_{1/2}$ 2 min). Various approaches have been used for the preparation of PET radiopharmaceuticals, where speed is of the essence (Ametamey *et al.*, 2008). Although many tracers commonly used for brain research are conveniently obtained by N-methylation with [^{11}C]methyliodide, more versatile synthetic approaches such as the Huisgen 1,3-dipolar cyclo-addition ('click' chemistry) are opening new vistas for radiochemistry (Wangler *et al.*, 2010). However, many potential tracers have failed to find widespread use, due to a variety of factors such as rapid peripheral metabolism, poor passage through the blood–brain barrier, inadequate process specificity, unfavourable binding kinetics, or inadequate specific binding relative to non-specific binding.

Based partly on historical precedents as well as the widespread availability of dopamine $D_{2/3}$ receptor PET ligands (e.g. [^{11}C]raclopride, [^{18}F]fallypride, see Figure 1), it is perhaps unsurprising that PET studies of drug addiction have tended to focus on the brain dopamine systems. However, the radiopharmacopeia targeting diverse types of 5-HT receptors is now in a phase of rapid development. The targeting of other biogenic amines and specific opioid peptide receptor subtypes lags lamentably behind, despite their promise for studies of addiction and personality. As in all pharmacological applications, the requirement of strict specificity is seldom met by available radiopharmaceuticals. For example, the study of dopamine receptors is still bedevilled by the lack of agents selecting between D_2 and D_3 receptor subtypes (Leopoldo *et al.*, 2009), and useful D_4 receptor ligands have yet to be developed. The widely used DOPA decarboxylase substrate [^{18}F]fluoro-*L*-dihydroxyphenylalanine (FDOPA, Figure 1C), while mainly trapped within dopaminergic neurons, also labels those containing 5-HT and noradrenaline (Brown *et al.*, 1999; Kumakura *et al.*, 2010).

General aspects of PET pharmacokinetics

Sequential frames in a dynamic three-hour PET recording with [^{18}F]fallypride show the progressive labelling of dopamine $D_{2/3}$ receptors in the human striatum (Figure 2); the task of kinetic analysis is to derive from these dynamic measurements an

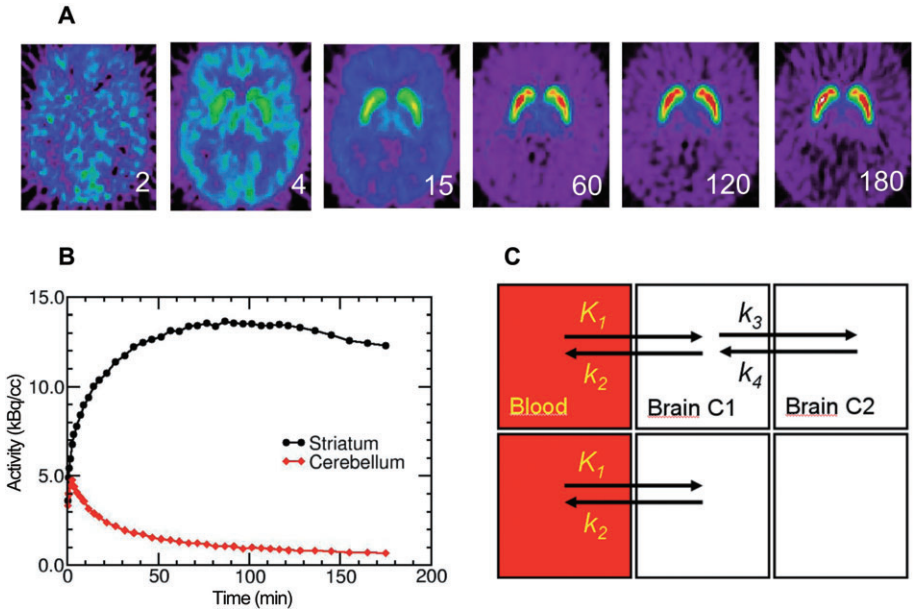

Figure 2

The time course of the uptake, binding and washout of the dopamine $D_{2/3}$ receptor antagonist [^{18}F]-fallypride in the brain of a healthy human subject. (A) Single frames from the 180 min dynamic recording, (B) the time activity curves extracted from striatum and cerebellum and (C) the compartmental model defining the reversible binding (upper boxes) and non-binding compartments (lower boxes).

estimate of the specific trapping, either in individual image elements (voxels) or in a defined volume of interest (VOI). This enables the construction of time–activity curves (TACs) containing information about initial clearance across the blood–brain barrier, binding in brain, and washout of the tracer (Figure 2B). Knowing the metabolite-corrected arterial input, as measured in serial blood samples, the brain TACs can be interpreted in terms of a model with binding and non-binding tissue compartments (Figure 2C). However, arterial blood sampling with HPLC correction of labelled metabolites is both invasive and time consuming to carry out. It is far easier to calculate specific binding in the defined VOI relative to the uptake in a reference region devoid of specific binding; this requirement is *approximately* met by the cerebellum in the case of [^{18}F]fallypride (Figure 2B) and indeed for quite a number of other receptor ligands.

The great preponderance of PET tracers is designed to interact with specific enzymes or receptors in brain. The prototype of these is [^{18}F]fluorodeoxyglucose (FDG), which is uniquely suited for measuring the cerebral metabolic rate (CMRglc) in living brain (Kuhl *et al.*, 1980). FDG-PET is an extension of the classical *ex vivo* autoradiographic method established in rat studies with [^{14}C]deoxyglucose (Sokoloff *et al.*, 1977), whereby the accumulation of radioactivity in brain is determined by the reversible facilitated diffusion of the tracer across the blood–brain barrier (mediated by a glucose transporter) and by the activity in brain of hexokinase, which is the rate-limiting step for glycolysis. As phosphorylated FDG does not proceed further along the glycolytic pathway, its trapping is *approximately* irreversible during a 45 min dynamic PET recording. This property, and near absence of plasma metabolites, makes FDG (with certain caveats) an ideal PET tracer. FDOPA kinetics is formally very similar to that of FDG, but is mechanistically different; partitioning of FDOPA across the blood–brain barrier is facilitated by an amino acid transporter, and retention within monoaminergic neurons is mediated by the local activity of the enzyme DOPA decarboxylase. Here the formal similarity of FDOPA with FDG ends, as the trapped [^{18}F]fluoropamine is eventually deaminated by monoamine oxidase (MAO); uncorrected diffusion from brain of resultant acidic metabolites can lead to a significant underestimation of the parameter of interest (Kumakura and Cumming, 2009). The penetration of a plasma metabolite into the brain adds further complexity to the interpretation of FDOPA-PET. Thus, FDOPA is a worst case scenario for kinetic modelling.

Whereas the enzymatic trapping of FDG and FDOPA in brain is, to the first approximation, irreversible, some tracers are receptor ligands of such high affinity that their association with the receptor can be considered irreversible for the time course of the PET recording. Thus, the net influx of [^{11}C]

3-*N*-methylspiperone (NMSP), a butyrophenone antagonist of dopamine $D_{2/3}$ receptors, can be considered irreversible in human brain during a 60 min dynamic PET recording (Wong *et al.*, 1986), although dissociation of bound [^{11}C]NMSP can be discerned in living pig brain (Rosa-Neto *et al.*, 2004). Most of the widely used PET and SPECT tracers for neuroreceptors share this property of reversibility, enabling the calculation of a steady-state parameter known as binding potential (*BP*), which is equivalent to the distribution volume ratio (DVR) in a binding region to that in a non-binding reference region, less one. When the mass of tracer is negligible, that is, for tracers of very high specific activity, the *BP* is proportional to the ratio of the Michaelis–Menten constants, that is, B_{max}/K_D.

The steady-state estimation of *BP* is readily obtained with 60 min PET recordings with [^{11}C]raclopride, a benzamide antagonist of dopamine $D_{2/3}$ receptors. Indeed, benzamides are among the mostly widely used tracers for neuropsychiatric PET studies, and have an especially useful property: vulnerability to competition from endogenous DA, which was first established using [^{11}C]raclopride-PET (Dewey *et al.*, 1993) and [^{123}I]IBZM-SPECT (Innis *et al.*, 1992) studies employing a challenge with the indirect dopamine agonist amphetamine. Other stimulants such as methamphetamine, cocaine, and methylphenidate also reduce the binding of the benzamide [^{18}F]4'-fluoroclebopride in monkey striatum (Mach *et al.*, 1997); even nicotine exerts a certain displacement of [^{11}C]raclopride binding in pig ventral striatum, although to a lesser extent than the psychostimulants (Cumming *et al.*, 2003). Amphetamine-evoked competition at dopamine $D_{2/3}$ receptors has also been demonstrated in a mouse microPET study with [^{18}F]fallypride and [^{18}F]DMFP (Rominger *et al.*, 2010), and in a rat microPET study with [^{11}C]raclopride (Pedersen *et al.*, 2007), where pre-treatment with a MAO inhibitor failed to produce the expected potentiation of dopamine release.

That the extent of benzamide displacement bears some relationship with the amount of dopamine release evoked by amphetamine is substantiated by animal studies employing microdialysis in conjunction with [^{123}I]IBZM-SPECT (Laruelle *et al.*, 1997) and [^{11}C]raclopride-PET (Endres *et al.*, 1997). However, not all released dopamine is alike with respect to competition. The displacement of [^{3}H]raclopride binding in rat striatum (measured *ex vivo*) shows a much steeper relationship with the increase in interstitial dopamine evoked by methamphetamine than was the case of nicotine, which releases dopamine by an entirely different mechanism (Kim and Han, 2009). Behavioural sensitization to amphetamine in monkeys has been linked to enhanced displacement of [^{123}I]IBZM by amphetamine challenge (Castner *et al.*, 2000), but behavioural cross-sensitization, as between cocaine and amphetamine (Liu *et al.*, 2007), has not yet been tested in PET or SPECT competition paradigms. In the case of cocaine addiction, the contribution of sensitization to the [^{11}C]raclopride competition paradigm is less clear. Although studies in animals support a pre-synaptic model of sensitization, corresponding studies in cocaine abusers show, on the contrary, an attenuation or blunting of competition in response to a cocaine challenge (Narendran and Martinez, 2008).

Dopaminergic transmission and subjective hedonic experience

It has sometimes been assumed that any pharmacological treatment increasing dopamine release in the ventral striatum should evoke a positive hedonic experience. Consistent with this view, intranasal administration of nicotine to habitual smokers, while not significantly reducing [^{11}C]raclopride binding in the group as a whole, did so in those subjects who reported a positive subjective experience (Montgomery *et al.*, 2007). Likewise, amphetamine-evoked [^{11}C]raclopride displacement in ventral striatum has been found to correlate with the degree of euphoria in normal healthy subjects (Drevets *et al.*, 2001), and subjects who self-report a 'high' following systemic administration of methylphenidate also show a significant displacement of [^{11}C]cocaine (Volkow *et al.*, 1999) and [^{11}C]methylphenidate (Volkow *et al.*, 1996) binding in striatum, which is indicative of increased competition from endogenous dopamine. Broadly similar findings have been observed in normal healthy volunteers subjected to psychosocial stress; those subjects with higher blood cortisol responses also reported greater positive subjective drug effects with amphetamine than did subjects with lower stress responses, which correlated positively with [^{11}C]raclopride displacement in the striatum (Wand *et al.*, 2007). In other words, the results of these challenge paradigms are potentially modifiable by behavioural traits and environmental influences. For example, trait impulsivity in human subjects predicts a blunted response to amphetamine in terms of [^{11}C]raclopride displacement in the right ventral striatum but nonetheless is associated with more pleasant subjective effects than experienced by non-impulsive subjects (Oswald *et al.*, 2007). Importantly, however, these effects were modified by history of life stress events, such that low-impulsive

subjects showed greater [^{11}C]raclopride displacement (suggestive of greater dopamine release) than did high impulsive subjects under low to moderate stress. Under conditions of high stress, both impulsivity groups showed a blunted displacement of [^{11}C]raclopride compared with subjects with no marked history of life stress. These findings thus suggest that attenuated displacement of [^{11}C]raclopride in the striatum may represent a neural endophenotype associated with risk for drug addiction, in a manner modified by life stress events. This conclusion is broadly compatible with a previous study in non-human primates showing the reinforcing effects of psychostimulant drugs to depend on the sensitivity of individuals to stressful social situations (Morgan *et al.*, 2002).

The imperfect relationship between enhanced dopamine transmission and subjective experience suggests that equating the messenger (dopamine) with the message (reward) is an over-simplification. In particular, cue-evoked craving in cocaine addicts has been linked with reduced [^{11}C]raclopride binding in proportion to the intensity of craving (Wong *et al.*, 2006a). Consistent with this finding, exposure of rats to a cocaine-conditioned environment has recently been found to produce a 20% reduction in striatal [^{11}C]raclopride binding (Schiffer *et al.*, 2009), an effect almost as great as that evoked by the drug itself. Nonetheless, pharmacologically evoked dopamine release is not, *per se,* a cue for drug seeking in cocaine addicts; although challenge with oral methylphenidate evoked the expected displacement of [^{11}C]raclopride binding in the ventral striatum of cocaine addicts, it did not evoke craving unless paired with cocaine-related cues (Volkow *et al.*, 2008b). Conditioned drug responses are widely believed to powerfully promote drug-seeking behaviour and contribute to drug craving and relapse in drug addicts (Childress *et al.*, 1999; Everitt and Robbins, 2005; Everitt *et al.*, 2008). Indeed, such responses can have a dramatic effect on dopamine release in the striatum. For example, exposing normal healthy male volunteers to a PET scanning suite where previously they had been exposed to amphetamine resulted in a remarkable displacement of [^{11}C]raclopride in the ventral striatum, of a magnitude as great as that produced by the drug itself (Boileau *et al.*, 2007).

PET studies of neural vulnerability mechanisms underlying addiction

Much research indicates that personality traits that encompass impulsivity and novelty/sensation-seeking can predispose to drug use and have a detrimental impact, speeding the development of drug addiction (Chakroun *et al.*, 2004; Dawe and Loxton, 2004; Nigg *et al.*, 2006; Verdejo-Garcia *et al.*, 2008). How in neural terms such traits could influence human drug addiction is poorly understood, but research in animals confirms that high levels of impulsivity is a strong predictor of intravenous cocaine and nicotine self-administration (Perry *et al.*, 2005; Dalley *et al.*, 2007; Diergaarde *et al.*, 2008). Our own research has focussed on a naturally occurring form of impulsivity in an out-bred strain of Lister hooded rats, measured by the increased propensity of some rats to 'jump the gun' and respond before the presentation of a visual cue on a 5-CSRTT (see Figure 3). The basic task requires rats to detect the spatial location of a brief light stimulus presented on a discrete trial basis at the rear of five open apertures (Robbins, 2002). Rats are rewarded with a small food pellet for a correct response and punished for responses made either in an adjacent aperture or too early, in the case of an impulsive response. The impulsive phenotype is present in a small but stable proportion of rats tested (~8–12%) and is exemplified by 'Zippy'; one of the original high-impulsive rats identified. Zippy was subsequently used as one of the founders in the establishment of a multi-generational inbred colony of high-impulsive rats (Schumann *et al.*, 2010).

A remarkable feature of high impulsivity in rats is that it predicts not only the escalation of intravenous cocaine and nicotine self-administration (Dalley *et al.*, 2007; Diergaarde *et al.*, 2008), but also a greatly increased propensity to develop compulsive cocaine taking (Belin *et al.*, 2008), and to relapse after a period of abstinence (Economidou *et al.*, 2009). Of relevance to a key hallmark of addiction specified in DSM-IV, we defined compulsive cocaine taking as drug intake that persists despite negative or adverse consequences, that is, the occasional delivery of positive punishment in the form of a mild electric foot shock (Everitt *et al.*, 2008; Belin *et al.*, 2008). Thus, trait-like impulsivity in rats appears to confer increased risk for drug addiction consistent with the clinical literature (Verdejo-Garcia *et al.*, 2008).

In a previous microPET study, impulsive rats showed significantly reduced [^{18}F]fallypride *BP* in the ventral striatum (including the NAcb), but not the caudate putamen (Dalley *et al.*, 2007). In addition, the [^{18}F]fallypride *BP* correlated inversely with impulsivity on the 5-CSRTT. This finding led to the suggestion that earlier reports of low dopamine $D_{2/3}$ receptor availability among detoxified cocaine users (Volkow *et al.*, 1997; Martinez *et al.*, 2004) may, to some extent at least, indicate a pre-existing trait, imparting a particular vulnerability for cocaine

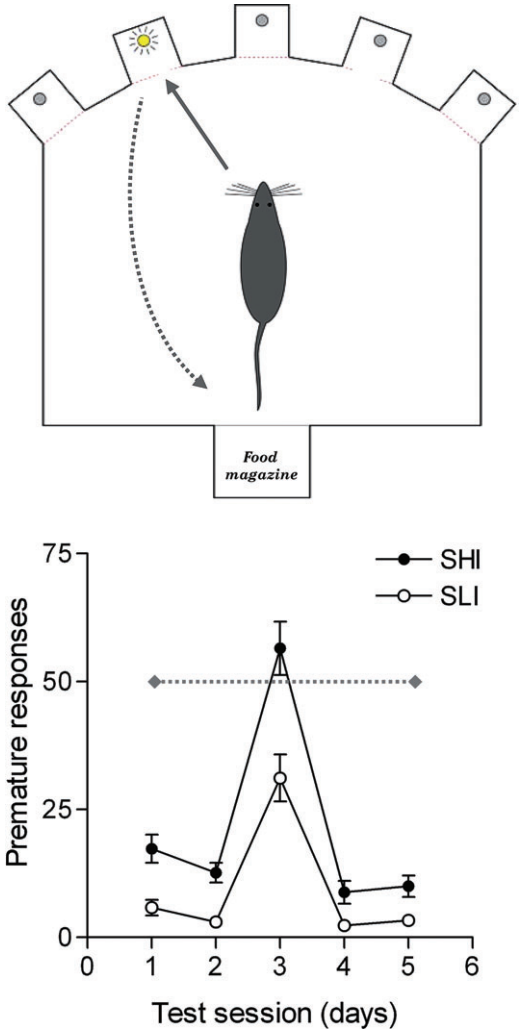

Figure 3

A schematic illustration of the five choice serial reaction time task (5-CSRTT) used to assess sustained visual attention and impulsivity in rats. Subjects are trained to locate the spatial position of a brief light stimulus with a nose-poke response and subsequently collect food reward from a forward facing food magazine. Nose-poke responses in an adjacent, non-illuminated aperture (deemed an 'incorrect' response) or responses made before the onset of the visual cue (deemed a 'premature' or 'impulsive' response) are signalled by the house-light being extinguished and the loss of food reward on that trial. Rats are selected as spontaneously high impulsive (SHI) if they make more than 50 premature responses during sessions where they are required to wait for 7 s (test day 3), rather than the expected 5 s (test days 1,2, 4 and 5), before the onset of the visual cue. Rats making 30 or fewer premature responses on such challenge sessions are categorized as spontaneously low impulsive (SLI).

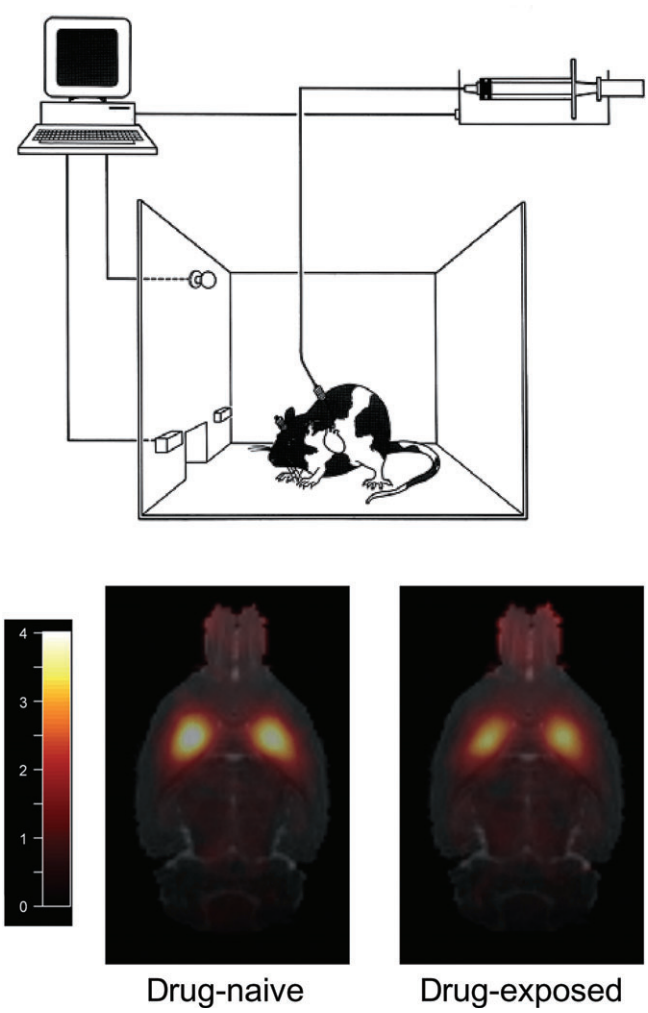

Figure 4

The self-administration paradigm used widely to assess the reinforcing effects of abused drugs like cocaine and amphetamine. In this procedure the intravenous delivery of drug is contingent on the rat pressing a lever while pressing a second lever on the opposite side of the chamber has no consequence. Rats withdrawn from intravenous d-amphetamine self-administration show a reduced uptake of the dopamine $D_{2/3}$ receptor antagonist [^{11}C]-raclopride in the caudate putamen, compared with rats administered saline. Shown are horizontal magnetic resonance images of the rat brain with co-registered PET. The scale bar denotes binding potential (*BP*) (reproduced with permission from Dalley *et al.*, 2009).

dependence, rather than a *state* acquired by chronic drug exposure. This conclusion is supported by the observation that low baseline availability of striatal dopamine $D_{2/3}$ receptors predicts high rates of cocaine self-administration in monkeys, which in turn further reduces the binding (Nader *et al.*, 2006), to an extent similar to what is observed in abstinent cocaine users (Volkow *et al.*, 1997; Martinez *et al.*, 2004) and rats with a previous history of intravenous amphetamine self-administration (see Figure 4). Conversely, high levels of [^{11}C]raclopride binding in abstemious relatives of patients with alcoholism appear to afford protection against the development of alcohol dependence (Volkow *et al.*, 2006). In addition, adenoviral-mediated overexpression of dopamine D_2 receptors attenuates the self-administration of alcohol in rats (Thanos *et al.*, 2001).

In general, these observations indicate that a given neurochemical state can be a predisposing factor in the development of drug addiction. Indeed, the converse experiment of the amphetamine challenge, in which endogenous dopamine is transiently depleted by administration of the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine, showed a blunted unmasking of striatal [^{11}C]raclopride binding among chronic cocaine users (Martinez *et al.*, 2009a). This observation of low basal dopamine tonus suggests that cocaine-dependent subjects may seek to self-medicate with cocaine an underlying deficiency state brought about by the drug itself. Indeed, amphetamine-evoked [^{11}C]raclopride binding changes are severely blunted in detoxified cocaine users (Volkow *et al.*, 1997; Martinez *et al.*, 2007). Moreover, higher social status is associated with higher baseline [^{11}C]raclopride binding in healthy volunteers (Martinez *et al.*, 2010), suggesting that social 'success' could mitigate against vulnerability towards drug dependence. Conversely, impulsive and antisocial psychopathic traits, which predispose towards drug seeking and addiction (Verdejo-Garcia *et al.*, 2008) are associated with greater reductions in [^{11}C]raclopride binding in the NAcb evoked by monetary or pharmaceutical rewards (Buckholtz *et al.*, 2010). Such findings have parallels with the treatment of Parkinson's disease patients with dopamine receptor agonists, which can sometimes provoke episodes of pathological gambling and other forms of compulsive behaviour (Steeves *et al.*, 2009). In these patients, performance of a gambling task evoked a greater decline in [^{11}C]raclopride binding in the ventral striatum than was seen in control subjects, consistent with greater dopamine release in this region (Steeves *et al.*, 2009).

Insufficiency of dopamine $D_{2/3}$ receptors in the NAcb, whether pre-existing or acquired, may contribute to the risk for relapse to drug seeking, which is intimately related to the experience of craving in response to drug-related cues (Childress *et al.*, 1999; Everitt *et al.*, 2008; Economidou *et al.*, 2009). Using a multi-modal imaging approach, Heinz and colleagues showed that the severity of cue-evoked craving, and cue-evoked fMRI activation of the anterior cingulate cortex was correlated with low availability of dopamine $D_{2/3}$ receptors measured with [^{18}F]DMFP-PET in the ventral striatum of detoxified alcoholics (Heinz *et al.*, 2004). In an extension of this work, the uptake of the presynaptic dopamine tracer FDOPA, while not reduced in a group of alcoholics, correlated inversely with the extent of craving and risk for relapse (Heinz *et al.*, 2005).

Dopamine in the frontal cerebral cortex operates quite differently from that in the basal ganglia where it is hypothesized to modulate switching between programmed behaviour and cognitive processes (van Schouwenburg *et al.*, 2010). Recently, it has been shown that a dopamine $D_{2/3}$ receptor agonist (bromocriptine) can improve flexible updating (switching) in high-impulsive individuals, supporting a top-down regulation of this cognitive process by the PFC (Cools *et al.*, 2007). However, molecular imaging of the contribution of cortical dopamine to fronto-executive cognition is technically challenging. Nevertheless, dopamine $D_{2/3}$ receptors can be detected in cerebral cortex and other regions of low abundance using the high affinity PET ligands [^{11}C]FLB 457 and [^{18}F]fallypride, or [^{123}I]epidepride-SPECT. In previous research, inventory measures of novelty-seeking were found to correlate negatively with [^{11}C]FLB 457 binding in the right insular cortex of normal subjects (Suhara *et al.*, 2001), and also in patients with Parkinson's disease (Kaasinen *et al.*, 2004). However, such findings are difficult to interpret as relatively little is known about the functional significance of dopamine in the insular cortex. A more tractable method to investigate cortical substrates of relevance to drug addiction and co-morbid brain disorders is with FDG-PET, which assesses cerebral metabolic rate (Kuhl *et al.*, 1980). Here, FDG uptake has been shown to be reduced in the anterior cingulate gyrus and OFC of opiate, methamphetamine and cocaine users (Volkow *et al.*, 1992; Galynker *et al.*, 2000; Kim *et al.*, 2009), as well as in alcoholic patients (Adams *et al.*, 1993). Such findings support the notion of impaired PFC function in human drug addicts leading to the loss of inhibitory control over maladaptive drug-seeking habits (Everitt *et al.*, 2008; Kalivas, 2008; Volkow *et al.*, 2008a).

With respect to novelty-(sensation-) seeking there has been some controversy about the involvement of brain dopamine and 5-HT. For example, in an [^{123}I]β-CIT-SPECT study of biogenic amine transporters in nearly 200 healthy young subjects, neither the early post-injection binding phase, said to reveal preferentially the 5-HT reuptake transporter (SERT), nor the binding at 24 h, which reveals mainly the dopamine uptake transporter (DAT), proved to correlate with sensation-seeking (Burke *et al.*, 2010). We have characterized the behavioural response to novelty of a mixed sex group of Göttingen minipigs, which were also investigated with [^{11}C]raclopride-PET (Lind *et al.*, 2005). The duration of contact with the novel objects proved to correlate with the amphetamine-evoked decline in striatal [^{11}C]raclopride *BP*; analysis by gender revealed this association to be driven by the male sub-group. In healthy human male subjects, scores in a test of sensation-seeking showed an inverted-U relation-

ship with baseline [^{11}C]raclopride binding in the striatum (Gjedde *et al.*, 2010). This observation may be related to the formal ambiguity of the PET end point, as low *BP* could arise from low receptor abundance (B_{max}) or from high apparent affinity (K_d^{app}, a function of basal occupancy by dopamine). Whereas striatal dopamine receptors are mostly post-synaptic, much of the binding of dopamine D_2 receptor ligands in mesencephalon reveals presynaptic autoreceptors, which regulate the activity of dopaminergic neurons. Given that mesencephalic [^{18}F]fallypride binding has been shown to correlate inversely with novelty-seeking in a large group of healthy volunteers (Zald *et al.*, 2008), tight feedback control of dopaminergic neurons may be unfavourable for the expression of the novelty-seeking trait. However, this conjecture serves as an instance of the need for more selective tracers.

Molecular imaging of ADHD and impulse control disorders

Insofar as ADHD is a predisposing factor for acquiring substance use disorders, ADHD might be considered a natural experiment in the biology of addiction. The contribution of brain dopamine to impulsivity in ADHD has been a matter of some controversy. As in all molecular imaging studies, the possible effects of medication on dopaminergic markers must be considered. Thus, for example, behavioural sensitization to amphetamine in monkeys has been linked to enhanced displacement of [^{123}I]IBZM in the amphetamine challenge paradigm (Castner *et al.*, 2000). Likewise, pre-exposure to amphetamine has been shown to enhance the amphetamine-evoked reduction in [^{11}C]raclopride binding in healthy human volunteers, especially in the ventral striatum (Boileau *et al.*, 2006). With this in mind, scores of inattention and impulsivity in drug-free adolescents with ADHD were found to correlate with the methylphenidate-evoked reduction in striatal [^{11}C]raclopride *BP* (Rosa-Neto *et al.*, 2005), particularly in low birth weight individuals with ADHD (Rosa Neto *et al.*, 2002). This intriguing finding was interpreted to reveal a functional overactivity, if not an actual superabundance, of DAT. In a study of never-medicated ADHD adults, baseline [^{11}C]raclopride *BP* in caudate was slightly lower than in the control group, and the methylphenidate-evoked decline was blunted, in proportion to the severity of self-reported symptoms (Volkow *et al.*, 2007b). Several differences might account for the disagreement of these two rather similar studies, such as the association of ADHD with low birth weight and the use of a more objective index of inattention in the former study. Nevertheless, the blunted response to methylphenidate does resonate with similar findings in human cocaine addicts (Narendran and Martinez, 2008), suggesting that partially overlapping neurobiological mechanisms may underlie ADHD and drug addiction.

In a recent [^{11}C]cocaine PET study of ADHD adults with no history of medication, the abundance of DAT was moderately reduced in the left NAcb and caudate nucleus, and, although [^{11}C]cocaine binding in the putamen did not differ between controls and ADHD subjects, it did correlate with inattentiveness in the ADHD group, and to a lesser extent also in the control group (Volkow *et al.*, 2007a). A subsequent study of a larger cohort of never-medicated ADHD patients (n = 53) replicated the finding of reduced [^{11}C]raclopride and [^{11}C]cocaine binding in the left NAcb and caudate, which extended to the midbrain as well in this study (Volkow *et al.*, 2009). This latter finding, which presumably involves somatodendritic sites on dopamine neurons, might suggest desensitization of autoreceptors regulating dopamine synthesis and release. If so, this would concur with a earlier report of increased FDOPA uptake in the mesencephalon of ADHD patients (Ernst *et al.*, 1999), although a subsequent FDOPA study found no such reductions in non-medicated patients, whereas reductions were observed throughout the basal ganglia of the methylphenidate-treated patients (Ludolph *et al.*, 2008), as noted above.

The clinical benefits of methylphenidate are likely mediated *via* blockade of DAT and/or noradrenaline transporters (NET) (Solanto, 2002; Fone and Nutt, 2005). Indeed, clinically useful doses of methylphenidate occupy approximately 50% of [^{11}C]-cocaine binding sites in the striatum of normal subjects (Volkow *et al.*, 1998), resulting in a 16% decline in the availability of [^{11}C]raclopride binding sites (Volkow *et al.*, 2002). In a SPECT study of 14 never-treated ADHD patients, [^{123}I]FP-CIT binding to DAT was 15% lower in the striatum, but did not differ in the thalamus, where the preponderant binding is to SERT (Hesse *et al.*, 2009). There was also no difference in DAT availability in a [^{11}C]PE2I-PET study of a group of 10, mostly never-medicated ADHD patients (Jucaite *et al.*, 2005). In contrast, DAT availability was 40% elevated in the left striatum in a [^{123}I]IPT-PET study of a relatively small ADHD group (Cheon *et al.*, 2003). Age-corrected DAT availability measured with [^{11}C]altropane-PET was, however, 15% higher in the caudate of a group of 21 never-medicated ADHD patients (Spencer *et al.*, 2007), and in a [^{99m}Tc]TRODAT-SPECT study (Dresel *et al.*, 2000). The same group subsequently claimed that responders to methylphenidate

therapy had low baseline DAT availability, while responders (12/18) had elevated DAT availability (Krause *et al.*, 2005). It is difficult to imagine a more inconsistent literature, which doubtless reflects the confounding effects of clinical heterogeneity, age and treatment effects in ADHD studies.

The role of dopamine D_1 receptors has been little investigated in the impulsivity and addiction literature. Although the binding of the dopamine D_1 antagonist [^{11}C]SCH23390 was reduced in the striatum of smokers (Dagher *et al.*, 2001), this observation was not corrected for previous alcohol consumption. More recently, the availability of striatal dopamine D_1 receptors in the striatum was shown not to differ between cocaine-dependent subjects and normal healthy volunteers (Martinez *et al.*, 2009b). Nonetheless, there was an inverse relationship between D_1 receptor binding in the ventral striatum and choice of cocaine over a monetary reward. Thus, dopamine D_1 receptor-mediated processes may confer vulnerability for cocaine addiction but further research would be needed to substantiate this notion.

Non-dopaminergic systems

Dopamine synthesis, receptors and transporters are the best studied neurochemical substrates in impulsivity and drug-seeking, but are not the sole players in this relationship. Efforts to develop PET ligands for NET have recently yielded useful agents of marginal utility, given the low abundance and specific binding (this may be an insuperable problem). In the first clinical application of NET-PET, the age-corrected binding of (S,S)-[^{11}C]O-methylreboxetine was found to be 50% higher in the thalamus and locus coeruleus of cocaine users (Ding *et al.*, 2010). In general, contributions of 5-HT to impulsivity and drug addiction are poorly documented. In a [^{11}C]DASB PET study of SERT, midbrain binding was reduced in patients with obsessive compulsive disorder and correlated inversely with symptom severity (Reimold *et al.*, 2007). In another study, significant reductions in SERT were found in the insular cortex and OFC (Matsumoto *et al.*, 2010). Serotonergic function can also be assessed using [^{18}F]altanserin, which binds to the post-synaptic $5HT_{2a}$ receptors that are abundantly present in cerebral cortex. However, to our knowledge, there have been no [^{18}F]altanserin-PET studies in the context of drug addiction. Such studies are justified by the fact that brain serotonergic mechanisms are strongly implicated in the form of impulsivity expressed by 'Zippy' (Dalley *et al.*, 2002; Puumala and Sirvio, 1998).

Very recently it has become possible to visualize cannabinoid CB_1 receptors in the living brain. In a large mixed gender population, a highly significant inverse relationship was found between cerebral binding of the CB_1 receptor inverse agonist [^{18}F]MK-9470 and novelty-seeking, as assessed by the Cloninger personality inventory (Van Laere *et al.*, 2009). This phenomenon extended throughout the grey matter, but was most significant in the right amygdala. In rat microPET studies, chronic injection of a high dose of nicotine was without effect on CB_1 receptor binding (Gerard *et al.*, 2010), whereas the anticonvulsant drug sodium valproate (but not levetiracetam) increased global [^{18}F]MK-9470 binding by one third (Goffin *et al.*, 2008); these studies serve as a model for longitudinal microPET studies of neurochemical interactions.

Molecular imaging studies of opioid receptors and indeed all G-protein-coupled receptors is complicated by the effects of affinity states. Thus, binding in living brain of the opioid receptor antagonist [^{11}C]diprenorphine is generally resistant to displacement by a number of opioid receptors agonists with a variety of subtype specificities, revealing the existence of a considerable reserve of non-functional opioid binding sites (Hume *et al.*, 2007). This property of agonists may impart the particular sensitivity of a dopamine $D_{2/3}$ agonist ligand to competition from endogenous dopamine (Cumming *et al.*, 2002; Narendran *et al.*, 2004), although the case for receptor reserve is less clearly established for dopamine receptors.

In normal subjects investigated with the non-selective opioid receptor antagonist ligand [^{18}F]fluoroethyl-diprenorphine, a positive correlation was found between binding in the bilateral ventral striatum and scores on the Cloninger personality dimension of reward dependence, an inventory that predicts drug-seeking propensity (Schreckenberger *et al.*, 2008). In a recent study, the distribution volume of [^{11}C]diprenorphine tended to be globally elevated in acutely abstinent alcoholics, in whom there was a positive correlation with alcohol craving, even after prolonged abstinence (Williams *et al.*, 2009). Others have shown the selective μ-opioid receptor agonist ligand [^{11}C]carfentanil can be almost completely displaced in heroin addicts treated with the partial μ receptor agonist, and κ/δ receptor antagonist buprenorphine (Greenwald *et al.*, 2003), and that high cortical binding of [^{11}C]carfentanil during acute abstinence predicts rapid relapse in cocaine users (Gorelick *et al.*, 2008).

In another of the lamentably few PET or SPECT studies of heroin addiction, striatal binding of the selective DAT ligand [^{11}C]CFT was found to be substantially reduced in patients on methadone

maintenance, which showed partial recovery with prolonged abstinence (Shi *et al.*, 2008). However, this need not indicate direct actions of heroin on dopamine transmission, as heroin does not appear to affect striatal [^{11}C]raclopride binding in heroin addicts (Daglish *et al.*, 2008).

While the modulation of drug addiction and impulsivity by the biogenic amines has been extensively examined by molecular imaging, corresponding methods for the excitatory amino acid receptors are poorly developed. The NMDA type ionotropic glutamate receptor, a key element in synaptic plasticity, is a heterotetramer, which presents at least three potential targets for molecular imaging: the cation channel, the modulatory glycine site, and specific NR2B subunits, which have been of particular interest in the study of neuroprotection. As recently reviewed, the search for adequate PET or SPECT tracers for these components of NMDA receptors has yet to yield useful agents (Sobrio *et al.*, 2010); ion channel agents tend only to recognize the open pores, which comprise only a tiny fraction of the total pool of NMDA receptors under normal physiological conditions. Glycine binding sites have been detected *in vivo*, but available imaging agents have very poor brain penetration (Matsumoto *et al.*, 2007), thus giving low specific signals. NR2B ligands tend to have poor solubility and although one PET ligand yielded specific labeling *in vivo*, it suffered from very rapid metabolism (Arstad *et al.*, 2006). Efforts to develop ligands for the metabotropic glutamate receptors (mGluR) have recently met with some success, perhaps reflecting the common structural elements of seven transmembrane domain G-protein receptors. Promising agents have been developed for the mGluR5 type receptor, which is highly expressed in striatum and hippocampus (Wyss *et al.*, 2007). There are very recent reports on mGluR1 receptor ligands for PET, one of which has proven adequate for occupancy studies in monkey brain (Hostetler *et al.*, 2010). Given the preliminary state of this research, it can only be anticipated that NMDA-type and MGluR ligands will eventually emerge as key agents for studies of drug-induced adaptation and synaptic plasticity in living brain (Jones and Bonci, 2005; Kauer and Malenka, 2007).

Conclusion

Although the development of molecular imaging has presented formidable technical problems, the effort is offset to a large degree by the provision of a privileged perspective on the neurochemical status of an individual. After 20 years of clinical and basic PET research of addiction, there has emerged a consensus that the transition to compulsive drug taking must entail pre-existing individual neurochemical risk factors, modified and exacerbated by drug exposure and environmental interactions, in the manner of a positive feedback loop with negative consequences for the individual. This model may be best tested in longitudinal molecular imaging studies of experimental animals with well-characterized behavioural traits, and well-documented exposure to psychostimulant drugs; as much as possible, future animal PET studies of addiction should emulate the natural history of human addiction, with consideration of factors thought to mediate the transition to habitual drug use by humans, such as trait-impulsivity, social stress, and environmental cues. Molecular imaging in addiction models has been bedevilled by the low spatial resolution of microPET (and microSPECT) relative to the size of relevant structures in the rodent brain. However, recent improvements in instrumentation now permit the distinction of functional and anatomical divisions of the striatum and PFC/OFC of humans and even rats. This is important because, within the last decade, interest has switched from the primary brain sites mediating the initial reinforcing effects of abused drugs such as the NAcb, to dorsal striatal systems underlying habitual drug use (Belin and Everitt, 2008; Everitt *et al.*, 2008; Belin *et al.*, 2009). However, very little is known of the neural and neurochemical substrates of *compulsivity,* which represents the final stage of drug addiction, and which may involve dysfunctional prefrontal cortical-striatal circuitry (Vanderschuren and Everitt, 2004; Everitt and Robbins, 2005; Porrino *et al.*, 2007; George and Koob, 2010). The shift from initial drug use to habitual and ultimately compulsive drug seeking appears to be critically influenced by predisposing neural and behavioural endophenotypes (e.g. low dopamine $D_{2/3}$ receptors, impulsivity) and by the progressive effects of repeated drug use on the network of topographically organized glutamatergic inputs to the basal ganglia from the PFC and OFC (Volkow *et al.*, 1992; Dalley *et al.*, 2007; Verdejo-Garcia *et al.*, 2008; Kalivas, 2009). Such changes presumably underlie the progressive decline in behavioural and cognitive control over drug-seeking behaviour that accompanies chronic drug exposure and therefore are major targets for future scientific investigation.

Great emphasis has been placed historically on the indisputable contributions of the brain dopamine systems to behavioural traits such as impulsivity as a predisposing variable in drug addiction. By turning the searchlight of molecular imaging towards biomarkers of other neurotransmitter

systems, especially 5-HT, noradrenaline, cannabinoids and opioid peptides, we should eventually obtain a more comprehensive and heuristically useful understanding of the underlying neurobiology of Zippy, which would be of inestimable translational value in deciphering the aetiology of human drug addiction.

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Conflict of interest

The authors have no conflicts of interest to declare.

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