Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Neurobiology

Translating positron emission tomography studies in animals to stimulant addiction: promises and pitfalls

Daniele Caprioli[1,2], Tim D Fryer[1,3], Stephen J Sawiak[1,3], Franklin I Aigbirhio[1,3] and Jeffrey W Dalley[1,2,4]

Addiction is a chronically relapsing brain disorder that insidiously affects the motivational and cognitive control systems of susceptible individuals. Clinical research over the last two decades has profited from the technique of positron emission tomography (PET), a non-invasive imaging technique that allows the longitudinal assessment of addiction-relevant biomarkers in current and former drug users. The vast majority of this research has unsurprisingly focused on the brain dopamine (DA) systems given their pivotal role in primary drug reinforcement and the rich abundance of dopaminergic PET tracers. However, the provocative failure of dopaminergic medications in addiction has fuelled the search for alternative treatments. This article considers current controversies in this field as well as prospects for elucidating neurotransmitter mechanisms in addiction beyond DA.

Addresses
[1] Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 3EB, UK
[2] Department of Psychology, University of Cambridge, Downing St, Cambridge CB2 3EB, UK
[3] Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK
[4] Department of Psychiatry, Addenbrooke's Hospital, University of Cambridge, Cambridge CB2 2QQ, UK

Corresponding author: Dalley, Jeffrey W (jwd20@cam.ac.uk)

Current Opinion in Neurobiology 2013, **23**:597–606

This review comes from a themed issue on **Addiction**

Edited by **Barry Everitt** and **Ulrike Heberlein**

For a complete overview see the Issue and the Editorial

Available online 9th May 2013

http://dx.doi.org/10.1016/j.conb.2013.04.003

Introduction

Before the ground-breaking discovery of intra-cranial self-stimulation by Olds and Milner almost six decades ago [1] the brain mechanisms of drug use and abuse were virtually unknown. Their fundamental research sparked unprecedented interest in dopamine (DA) as a major neuromodulator of the brain reward systems [2]. In parallel, the emergence of positron emission tomography (PET), a powerful non-invasive imaging technique widely used to quantitatively map the temporally variant concentration of a radiolabelled compound across the brain, provided unequivocal confirmation that DA transmission is perturbed in some way in addicts [3–7]. However, as this review points out, DA mechanisms alone are unlikely to explain the full repertoire of this complex brain disorder. Firstly, we outline how PET has advanced our understanding of the neural correlates of chronic drug use, before going on to describe the controversies and limitations of this research. Lastly, we discuss recent PET studies in rodents and non-human primates with translational relevance to the aetiology and development of new treatments for substance use disorders in humans.

A synopsis of PET research in stimulant addiction

The precise role of DA in pathological forms of motivation, including addiction, is still a matter of debate. One longstanding view holds that DA mediates the hedonic effects of addictive drugs, but this theory is contentious [8], despite some support from PET studies and preclinical evidence that all abused drugs acutely increase DA release in the nucleus accumbens (NAcb) [9]. Thus, subjects who self-reported a 'high' following systemic treatment with methylphenidate also showed a significant displacement of [^{11}C]cocaine binding in the striatum [10], indicative of increased competition from endogenous DA in this region. Further, habitual smokers only reported a positive subjective response to nicotine when this was accompanied by a reduction in binding of [^{11}C]raclopride, a D2/D3 receptor antagonist (see Table 1) [11].

However, other PET findings have not been so clear-cut. For example, healthy subjects exhibiting higher stress responses, as measured by blood cortisol levels, reported amphetamine to be more pleasant than subjects with lower stress responses, which correlated positively with [^{11}C]raclopride displacement in the striatum [12]. Other traits such as impulsivity, however, predicted a blunted response to amphetamine in terms of [^{11}C]raclopride displacement in the right ventral striatum, but impulsive subjects nonetheless reported more pleasant subjective effects than non-impulsive subjects [13]. Furthermore, simply exposing normal healthy male volunteers to a PET imaging suite where previously they had been exposed to amphetamine was sufficient to displace [^{11}C]raclopride in the ventral striatum, of a magnitude as great as that produced by the drug itself [14]. These results suggest an imperfect relationship between DA neurotransmission and subjective drug effects and one

Table 1

Commonly used radioligands and their primary target binding sites

Target	Tracer	Action	Compound description
Cerebral blood flow	[^{15}O]H_2O		[^{15}O]H_2O
Glucose metabolism	[^{18}F]FDG		2-Deoxy-2-(^{18}F)fluoro-D-glucose
Dopamine (DA)	[^{18}F]FDOPA	DA synthesis	3,4-Dihydroxy-6-(^{18}F)-fluoro-L-phenylalanine
	[^{99m}Tc]-TRODAT-1β-CFT	DA transporter (DAT)	[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)]-(^{99m}Tc)
	[^{18}F]FECNT		2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-(^{18}F)fluoroethyl)nortropane
	[^{11}C]β-CFT		(^{11}C)-2β-carbomethoxy-3β-Itropane
	[^{11}C]Cocaine		(^{11}C)methyl (1*R*,2*R*,3*S*,5*S*)-3-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid
	[^{11}C]MPH		(^{11}C)dl-threo-methylphenidate
	[^{11}C]SCH 23390	D1-like receptor antagonist	(*R*)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-(^{11}C)methyl-5-phenyl-1*H*-3-benzazepin-7-ol
	[^{11}C]NNC 112		(+)-8-Chloro-5-(7-benzofuranyl)-7-hydroxy-3-(^{11}C)methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine
	[^{125}I]IBZM	D2-like receptor antagonist	(*S*)-3-(^{125}I)-iodo-*N*-[(1-ethyl-2-pyrrolidinyl)] methyl-2-hydroxy-6-methoxybenzamide
	[^{11}C]raclopride	Antagonist	3,5-Dichloro-*N*-{[(2*S*)-1-ethylpyrrolidin-2-yl]methyl}-2-hydroxy-6-(^{11}C)methoxybenzamide
	[^{18}F]fallypride	Antagonist	(*S*)-*N*-((1-Allyl-2-pyrrolidinyl)methyl)-5-(3-(^{18}F)fluoropropyl)-2,3-dimethoxybenzamide
	[^{18}F]FCP	Antagonist	4′-(^{18}F)fluoroclebopride
Vesicular monoamine transporter (VMAT)	[^{11}C]DTBZ		(+)(^{11}C)dihydrotetrabenazine
Serotonin (5-HT)	[^{11}C]McN5652	5-HT transporter (SERT)	*trans*-(+)1,2,3,5,6,10b-Hexahydro-6-(4-((^{11}C)methylthio)-phenyl)pyrrolo-(2,1-a)-isoquinoline
Opioid	[^{11}C]carfentanil	μ-opioid receptor agonist	4-((1-Oxopropyl)-phenylamino)-1-(2-phenylethyl)-4-(^{11}C)piperidinecarboxylic acid methyl ester
	[^{18}F]FDPN	(μ-opioid antagonist/ δ-opioid-κ-opioid agonist)	6-*O*-(2-(^{18}F)fluoroethyl)-6-*O*-desmethyldiprenorphine)

which is remarkably modifiable by behavioural traits and environmental cues.

As the primary target of cocaine and other stimulant drugs, PET research has logically focused on the DA transporter (DAT). However, results to date suggest that compensatory changes in DAT regulation depend on several variables including the actual drug of abuse, severity of use and duration of abstinence. In abstinent cocaine addicts, binding to DAT was increased in the striatum compared with healthy controls [15,16]. However, in abstinent methamphetamine (MA) abusers, DAT showed striking reductions in many brain regions including the NAcb, striatum, anterior prefrontal cortex (PFC), orbitofrontal cortex (OFC), dorsolateral PFC and amygdala compared with healthy controls [17–20], a deficit that recovered with long-term abstinence [21]. Interestingly, when acutely administered, the euphoric effects of intravenous cocaine strongly correlated with the degree of DAT occupancy in the striatum [22]. However, in general, the interpretation of DAT binding in chronic addicts is complicated by underlying compensatory processes that differ according to drug history and probably other factors as well [23]. Nevertheless, mutations of the DAT gene powerfully modulate limbic neural responses to smoking cues and may, as a result, contribute to craving and other aspects of smoking addiction [24].

Less controversial effects are reported with regard to striatal D2/D3 receptors which show a robust downregulation in stimulant addicts [18,25]. This abnormality can persist for many months following drug-withdrawal [26–28,29•] and, notably, can predict the likelihood for relapse in former MA abusers [30••]. However, MA addicts not only show reduced D2/D3 receptor densities, but they also show higher levels of impulsivity than healthy control subjects [31]. A recent [^{18}F]fallypride-PET study has confirmed this result, reporting that lower D2/D3 autoreceptor binding in the midbrain was associated with greater questionnaire-measured impulsivity [32••]. A key question, though, is whether these effects are a consequence of stimulant use. Recent evidence suggests that perhaps they are not, since first-degree relatives of stimulant abusers also showed increased impulsivity [33], implying that impulsivity may be a trait marker that shapes individual predisposition for addiction.