Positron emission tomography (PET) is opening new avenues for the investigation of the neurochemical disturbances underlying drug abuse and addiction and the in vivo *mechanisms by which medications might ameliorate these conditions*

Imaging addiction with PET: is insight in sight?

Wynne K. Schiffer, Dianne E. Lee, Jonathan D. Brodie, and Stephen L. Dewey

Neurochemical imaging studies can identify molecular targets of abused drugs and link them to the underlying pathology associated with behaviors such as drug dependence, addiction and withdrawal. positron emission tomography (PET) is opening new avenues for the investigation of the neurochemical disturbances underlying drug abuse and addiction and the *in vivo* mechanisms by which medications might ameliorate these conditions. PET can identify vulnerable human populations, treatment strategies and monitor treatment efficacy. Thus, with this tool and the knowledge it provides, the potential for developing novel drugs and treatment strategies for drug addiction is now close at hand.

Wynne K. Schiffer
Stephen L. Dewey
Department of Neurobiology & Behavior,
Stony Brook University,
Stony Brook,
NY 11794,
USA
Wynne K. Schiffer
Dianne E. Lee
Stephen L. Dewey
Chemistry Department,
Brookhaven National Laboratory,
Upton,
NY 11973,
USA
Jonathan D. Brodie
Marvin Stern Professor of Psychiatry,
New York University School of Medicine,
550 First Avenue,
New York,
NY 10016,
USA
*e-mail: wynne@bnl.gov

Medical imaging helps physicians and researchers visualize or diagnose disease without having to rely on external examination or exploratory surgery. The field can be broadly divided into two categories, depending on whether the image is captured from a device that is inside the body or outside the body. From inside the body, endoscopic (from the Greek endos, within) approaches use a camera attached to a tube or capsule to visualize lesions on internal organs. From outside the body, tomographic (from the Greek tomos, slice) approaches use a camera to visualize atomic events such as radioactive decay or magnetic spin with little or no invasiveness. Tomographic approaches have greatly enhanced our understanding of the anatomical and functional changes in the human brain following chronic exposure to drugs of abuse.

Whether the tomographic technique is used to visualize anatomy or function, by definition, these approaches share several common features. In each case, the patient or participant lies inside a tomograph that takes planar pictures of two-dimensional slices through the body. Next, these two-dimensional pictures are assembled, or reconstructed, into a three-dimensional image. Beyond this, the different tomographic approaches become more specialized to measure specific

WYNNE K. SCHIFFER

Wynne Schiffer was born in Casper, Wyoming and studied psychology and neuroscience at The Colorado College in Colorado Springs, Colorado. In 2004, she received her Ph.D. from the Department of Neurobiology and Behavior at Stony Brook University in New York. During her doctoral study, Schiffer developed a combined positron emission tomography (PET) imaging and microdialysis approach to study neurotransmitter interactions with a host of different radiotracers in small animals. Schiffer is currently an Assistant Chemist at Brookhaven National Laboratory in New York.

DIANNE E. LEE

JONATHAN D. BRODIE

STEPHEN L. DEWEY

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GLOSSARY

Anatomical imaging: Imaging techniques for analyzing the anatomic relationships of organs, cells and subcellular structures. Juxtaposed with *functional* imaging, these include anatomical MRI, CTor X-Ray.
Computerized (axial) tomography (CT or CAT): A computer assisted technique that generates visual cross-sectional images by exposing a subject to an x-ray beam that rotates around the subject and then records those beams which pass through the body.
Conditioned place preference (CPP): A model of environmental-cue induced craving in which animals experience two distinct neutral environments that are paired spatially and temporally with drug treatment. The animal is later given an opportunity to choose to enter and explore either environment, and the time spent in the drug-paired environment is considered an index of the reinforcing value of the drug.
Dopamine (DA): A neurotransmitter that plays a fundamental role in reward and in the reinforcing properties of abused drugs.
Functional imaging: Techniques to obtain images that represent physiological and metabolic processes performed by organs in the body. Juxtaposed with *anatomical* imaging, these include PET, SPECT and functional MRI.
Gamma aminobutyric acid (GABA): A neurotransmitter that inhibits the generation of new nerve signals in the receiving (post-synaptic) neuron.
Glutamate: A neurotransmitter that promotes the generation of new nerve signals in the receiving (post-synaptic) neuron.
***In vivo* microdialysis:** A technique used to directly measure the *in vivo* release of neurotransmitters in brain tissue.
Magnetic resonance imaging (MRI): A computer assisted technique for creating cross-sectional images by exposing a subject to radio waves in the presence of a powerful magnetic field and measuring signals emitted by certain atoms in the affected area in response to the magnetic field.
Mesolimbic reward system: A part of the motivational system that regulates responses to natural reinforcers and drug mediated rewards. It originates in the midbrain, comprised of the ventral tegmental area (VTA) and substantia nigra (SNig), and projects to the striatum, including the nucleus accumbens (NAcc). The NAcc is the region where reward-induced changes in dopamine transmission occur.
Neural plasticity: The phenomenon that changes in large numbers of neurons and very large numbers of synapses are involved in the brain's adaptive processes.
Positive reinforcement: Rewards (drug or non-drug) which increase the frequency of the behavior that delivers them.
Positron emission tomography (PET): A computer-assisted technique for generating cross-sectional images of a subject by measuring the radioactivity released by radiotracers in the body.
Reconstruction: Process of assembling the two dimensional frames obtained from a tomographic scan into a three- or four- dimensional image.
Resolution: The smallest detectible distance between two points.
Single photon emission computerized tomography (SPECT): A computer-assisted technique to generate cross-sectional images; combines the use of radiotracers with computed tomography.

processes. Computed tomography (CT, or computerized axial tomography, CAT) creates images based on the contrasting density between bone and tissue, and is especially useful for detecting bone fractures. Structural or anatomical magnetic resonance imaging (aMRI) uses a magnetic field and periodic pulses to spin hydrogen nuclei, and then uses their relaxation to deduce variations in tissue density caused by lesions or changes in the volume of brain structures that might be vulnerable to a specific disease.

Related techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional MRI (fMRI) have the unique ability to measure changes in the function of the human body. In this way, PET, SPECT and fMRI are very different from anatomical imaging methods such as CT or aMRI. Whereas the latter methods produce a single image at an isolated point in time, functional approaches can map molecular kinetics and enzymatic reactions over relatively short intervals of time. For example, in Figure 1 the anatomical (CT and aMRI) and functional (PET) images from a methamphetamine addict illustrate the notion that changes in brain function are not always reflected by measurable changes in brain anatomy, at least at the present state-of-the-art resolution.

PET has traditionally been used to study drug addiction by tracking an addictive drug in the brain or measuring the acute neurochemical response to an abused drug. However, the potential for PET extends beyond this. There are several experimental paradigms that have been developed and are widely used to study drug abuse and its consequences (Box 1). With these strategies, PET becomes a powerful tool to determine drug action and also how these events might contribute to reinforcement or reward. This review provides a brief overview of the nature of drug reward as it relates to identified changes in behavior and brain chemistry, and discusses the importance of PET in elucidating the subtle plasticity of the brain and its vulnerability to chronic drug exposure. Finally, as a result of the information gained from PET studies, the development of novel approaches to treating drug abuse and addiction is highlighted.

Addiction in the context of a central reward system

Drug dependence and drug addiction can be characterized by varying degrees of severity, ranging from occasional drug taking to excessive and potentially life-threatening drug use [1]. However, it is not known how much drug taking is required to produce these classic behavioral manifestations, nor has it been established how much variability there is from one patient to the next, or from one addictive drug to the next. Addictive drugs have well-established effects on brain circuits involved in the control of motivated and learned behaviors, which are well conserved from animal models to human behavior.

Translational neuroscience: addictive behaviors span from mouse to man

Part of the mystery surrounding the biological basis of drug abuse that has especially benefited from PET is the phenomenon that drugs with few or no common molecular features produce a very similar behavioral profile in humans and animals. For example, studies of [^{11}C]-cocaine demonstrated that its initial target in the human brain was distinct from that of [^{11}C]-nicotine, both of which significantly differed from [^{11}C]-carfentanil, an analog of heroin [2,3]. These studies substantiated preclinical work showing that cocaine, a stimulant that causes the heart to race, and carfentanil (heroin-like), a pain–relieving sedative, possess different molecular and biochemical properties, despite a common collection of dependence-like behaviors.

Studies using this type of self-administration schedule have shown that animals will work very hard for the

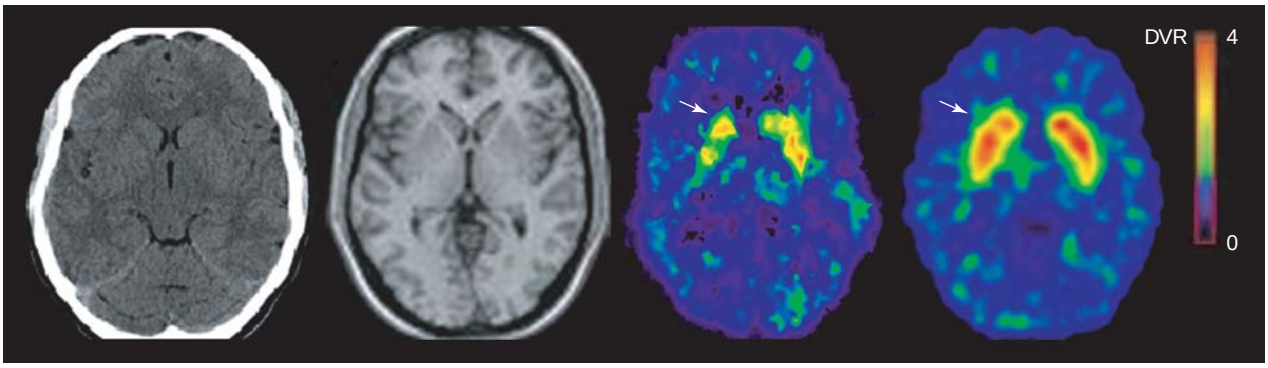

FIGURE 1

Anatomical versus functional brain images. Both the CT and aMRI scans appear to be without anatomical pathology, yet the PET scan shows a tremendous deficit in the function of the brain chemical, dopamine, in the methamphetamine abuser. Chronic exposure to drugs of abuse causes profound changes in brain processing which are invisible to standard anatomical imaging techniques, yet unmistakable with PET measures of neurochemical and metabolic function.

positive reinforcement of cocaine or heroin. Other animal models show that they also prefer environments associated with abused drugs (conditioned place preference, ref. [4]). More striking are the studies of triggered relapse, as this appears to be a significant barrier to drug abuse treatment [5]. After an abused drug is removed, animals will cease to labor for its effects. However a single administration of the same drug or a completely unrelated, stressful event, can trigger the animal to press the lever again, as much as months after cessation [5]. These animal models have established that drugs of abuse all produce a strikingly similar behavioral profile.

The notion of a centralized reward system involving dopamine implies that potential treatments can focus on a common molecular target, as opposed to specialized treatments for each abused compound or behavior. This provides an attractive option to the pharmaceutical industry, long hesitant to jump into the addiction treatment market because of a misperception of unacceptably low profit margins.

Neurotransmitter interactions within a common reward pathway

Addictive drugs are thought to stimulate the central reward circuit, the mesolimbic reward system, with a potency greater than any natural reward such as food or sex. A key component of this circuit is dopamine, which is contained in neurons located in the ventral tegmental area (VTA) and projecting to the corpus striatum. This pathway is required for the reinforcing effects of drugs [6]. Animals with lesions to any location within the circuit no longer show interest in substances of abuse [7]. However, the role of the mesolimbic dopamine system in non-stimulant drug reward and in positive emotion has not been clearly established. More recent models have focused on a significant role for the mesolimbic dopamine system in the anticipation of reward [8].

However, if GABA is released from the pre-synaptic axon and binds to GABA receptors on the post-synaptic dendrite, this inhibitory neurotransmitter prevents the generation of a new nerve signal. Glutamate and GABA are classic excitatory and inhibitory neurotransmitters, respectively.

In summary, brain circuits function in concert to control biological, behavioral and humoral processes by modulating the transfer of information through complex interactions. These interactions serve to maintain a functional state of homeostasis. When the ability to maintain homeostasis becomes compromised, addiction can result. In this regard, measuring the functional responsiveness of dopamine neurons to stimulation might ultimately be directed toward identifying populations that are vulnerable to the development of tolerance or sensitization associated with the progression from acute drug use to chronic drug abuse.

Using PET to study drug action and understand drug abuse

PET studies can be used to investigate several components of the addictive process, from the initial site of drug action to the impact of drug abuse on many different chemical systems. Another advantage is that the same research subject can be scanned over days and years. PET scans, then, are primarily geared toward establishing the potential events such as a change in receptor expression or neurotransmitter responsiveness through which drug administration produces tolerance, dependence and finally, addiction.

Because [^{11}C]-raclopride competes with dopamine for receptor binding sites (see Box 1 for more detail), its displacement can be used as an indirect assay of synaptic

BOX 1

Experimental procedures for PET studies of drug action

At the heart of PET and its ability to measure brain function is the radioactive tracer molecule, or radiotracer. A radiotracer is any molecule of interest (for example, the cocaine molecule) in which stable atoms are replaced with unstable, radioactive atoms (in this case [^{11}C]-cocaine). The radiotracer can be intravenously injected, inhaled or taken orally, depending on the intent of the experiment. The isotopes of the radiotracer emit positrons in a rare type of radioactive decay. After traveling less than a millimeter, the positron collides with an electron and annihilates, producing a pair of gamma ray photons that project out of the brain in opposite directions. These are detected by a ring of scintillator crystals surrounding the participant's head. The scintillation crystals allow the gamma photon signal to be detected and amplified by photomultiplier tubes, which store and transmit the resulting signal to a computer. Key to the technique is the coincidental detection of the pair of gamma photons: those which are not simultaneously detected (separated by a few nanoseconds) are ignored. By measuring coincidental gamma photons, their origin in the brain can be plotted and radiotracer uptake in regions of interest (ROIs) can be quantified.

Isotopes of familiar elements such as carbon, oxygen, fluorine or nitrogen are commonly incorporated into radiotracers because they are chemically very similar to the non-radioactive nuclides, so most biological processes treat them in a near identical way. Organic radiotracers most often incorporate carbon-11 (half-life [$t_{1/2}$] = 20 min) or fluorine-18 ($t_{1/2}$ = 110 min), because the radiation dosimetry for these short-lived isotopes is low. Therefore, the pharmacokinetic and pharmacodynamic properties of each radiotracer, or the speed and biological impact of each, closely resemble the endogenous compound whose actions these radiotracers probe or mimic.

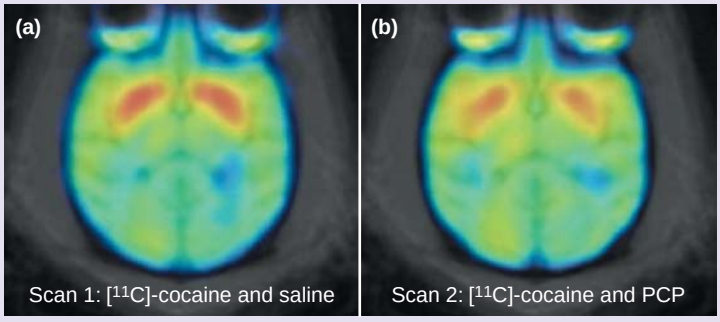

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FIGURE I

PET studies of drug action help understand its abuse. Primate PET experiments of [^{11}C]-cocaine binding alone **(a)** and its displacement when co-injected with phencyclidine **(b)**. These studies suggest that the rewarding properties of PCP share similar underlying mechanisms with cocaine.

PET strategies to study abused drugs can be broadly divided into those that measure the dynamic activity of receptors and neurotransmitters, or those that give information about blood flow and metabolism in specific areas of the brain.

These experiments can be performed at rest or after a pharmacologic challenge with a drug of abuse or drug/treatment combination. When challenges are used, PET experiments are usually performed using two consecutive scans in a paired-bolus paradigm. The first scan occurs during a resting state to assess radiotracer binding at baseline. The second scan is performed during the challenge condition, after a stimulus. In these experiments, the stimulus can either be a drug that will compete directly with the radiotracer for binding sites or will produce a change in neurotransmitter that will compete with the radiotracer for binding sites.

For example, [^{11}C]-cocaine can be used with PET in a paired-bolus design to assess the similarities between cocaine and other drugs that may potentially be addictive. Cocaine's reinforcing effects are mediated by blockade of monoamine transporter

TABLE I

Strategy	Description
1	A compound can be labeled and administered, allowing a direct measure of its distribution in the brain and other organs. Many drugs of abuse have been labeled directly (see Table 1)
2	At a 'tracer' dose (that which occupies only a small fraction of the available binding sites, 1/1000 of a pharmacologically active dose in humans), the PET image may reflect the local concentration of drug binding sites.
3	Competition between an abused drug and a different radiotracer that goes to the same site can be measured, making it possible to estimate the number of receptors that are occupied by the abused drug and the relationship of this action to feelings of euphoria (Figure II).
4	Competition between a receptor-specific radiotracer and a naturally occurring chemical for a receptor site can give an index of the activity of that natural chemical, through the inverse relationship of radiotracer binding.
5	Competition approaches can also assess the utility of potential treatments for blocking reward-related increases in mesolimbic dopamine (Figure II).
6	PET can be used to measure fluctuations in glucose metabolism as neurons are activated and deactivated. With the radiotracer, 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG), PET can measure the rate at which glucose is metabolized (local metabolic rate of glucose utilization, LMRGlu), providing an index of changes in energy demand in specific areas of grey matter in the brain during a mental activity such as drug craving.
7	Regional cerebral blood flow (rCBF) can be measured by tracking the activity of [^{15}O]-water to brain areas that are activated by a task.

dopamine release in response to drugs of abuse. Alternatively, when dopamine is depleted with drugs like reserpine or α-methyl-para-tyrosine (AMPT), [^{11}C]-raclopride can be used to measure D_2 receptor density [9]. Another commonly used clinical radiotracer is [^{18}F]-fluorodeoxyglucose (^{18}FDG), an analog of glucose. In Figure 2, both of these radiotracers have been used to show that chronic cocaine abuse produces prolonged effects on the energy demand of specific brain areas (particularly frontal and striatal regions), and that [^{11}C]-raclopride binding sites disappear after years of hard use [10]. These studies have shown that impairments in striatal dopamine function might be related to metabolic deficits in distant, frontal brain regions [11]. It is unknown how much drug use is required

proteins, preventing presynaptic reuptake. This action mediates the reward associated with cocaine abuse. Drugs that block monoamine transporters are usually self-administered. However, some drugs may possess primary targets in the brain that are not on monoamine-containing neurons. Phencyclidine (PCP, 'angel dust') is one such drug that binds primarily to NMDA receptors on glutamate neurons. However, PCP shares with cocaine the ability to bind to monoamine transporters (Figure I). Indeed, PET studies show that PCP is potent enough to displace [^{11}C]-cocaine (Figure I), suggesting that its impact on the dopamine component of the reward system is similar to cocaine [30]. This may explain why PCP is self-administered, although evidence from other, more selective NMDA glutamate receptor antagonists, is inconsistent [28]. The different strategies to use PET in studies of drug abuse are listed in Table I.

Another strategy that has been useful to the study and treatment of drug abuse capitalizes on the weak binding of specific radiotracers to their receptor targets. In this case, neurotransmitter and radiotracer compete for binding sites, and changes in neurotransmitter are reflected as inverse change in radiotracer binding [18,76,77]. For example, [^{11}C]-raclopride has been used extensively to probe changes in synaptic dopamine induced by reinforcing drugs. Figure II uses parametric distribution volume ratio (DVR) images to describe ^{11}C-raclopride binding in two primates at baseline, following a cocaine challenge, and again given cocaine 2.5 h after receiving γ-vinyl GABA (GVG). From Frame (a) to Frame (b), it is evident that increases in synaptic dopamine produced by cocaine prevent ^{11}C-raclopride from binding. In Frame (c), prior treatment with GVG inhibits this dopamine pulse, and ^{11}C-raclopride binds to the same extent as in the baseline condition [18].

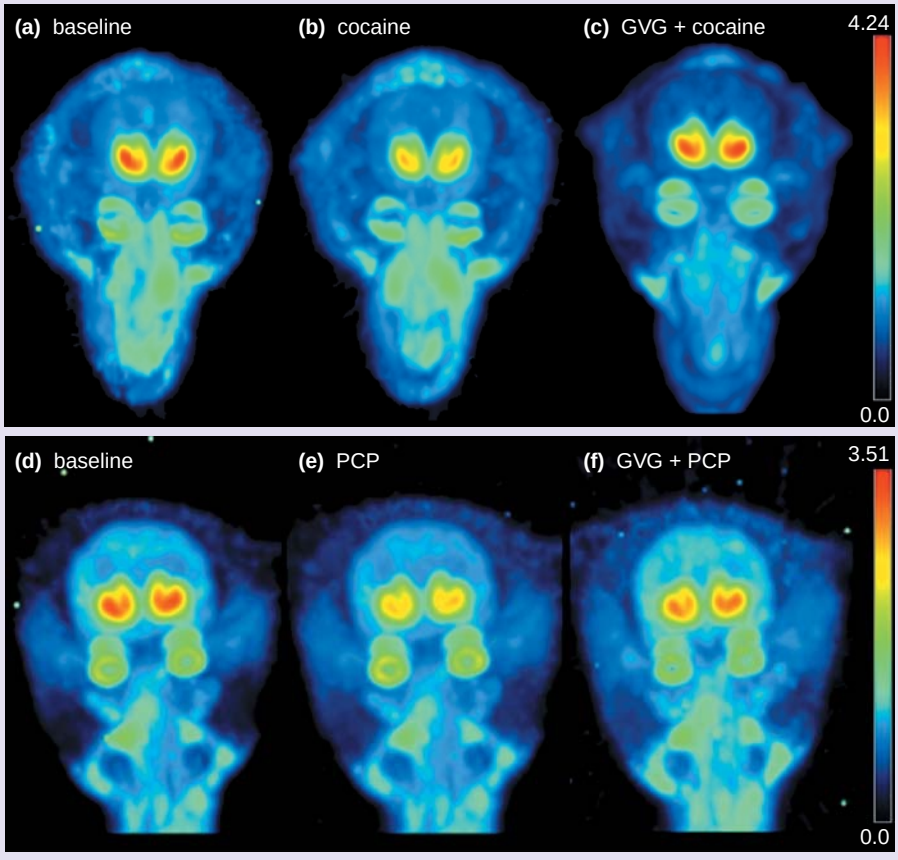

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FIGURE II

Using PET to develop a treatment for substance abuse. GVG pretreatment blocks cocaine and PCP-induced decreases in [^{11}C]-raclopride binding. Volume-rendered parametric images of papio anubis baboons undergoing identical protocols as those used to assess the effects of addictive compounds on dopaminergic systems in humans. Decreases in [^{11}C]-raclopride binding reflect increases in dopamine. At baseline, [^{11}C]-raclopride binds to those dopamine D_2 receptors that are not already bound with dopamine (frames a and d). As dopamine increases following psychostimulant administration, [^{11}C]-raclopride binding decreases (frames b and e). These effects are blocked by pretreatment with GVG (frames c and f). Parametric images are colored using the extended rainbow color scale (far right) where red represents the image pixels with the highest DVR values.

to produce this effect, nor has it been established whether these changes return to normal.

Box 1 also presents the way in which PET can be used to measure changes in neurotransmitter release within the synapse. PET studies of dopamine-induced changes in [^{11}C]-raclopride binding become especially relevant to drug abuse in light of the compelling proposal that, at least in rodents, drugs abused by humans increase dopamine release proportionally with their abuse liability or locomotor activating ability [12]. According to this notion, the extent to which a drug increases dopamine in the mesolimbic reward system is closely related to that particular drug's abuse liability. In Table 1, studies using [^{11}C]-raclopride to assess drug-induced changes in dopamine

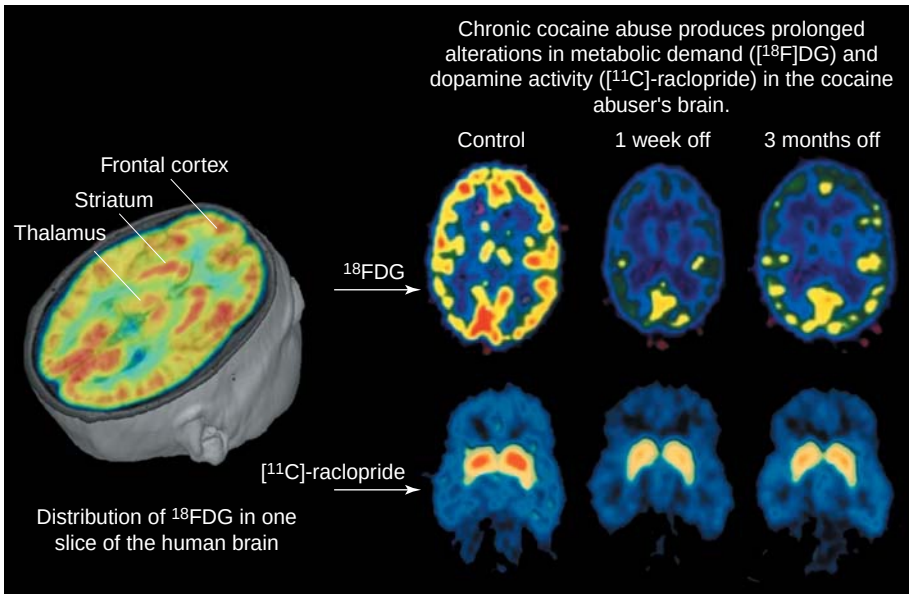


FIGURE 2

Capturing chemical and metabolic recovery from drug abuse using PET. Images courtesy of Nora Volkow.

are listed (where available). According to the hypothesis that the magnitude of drug-induced change in dopamine is correlated with its abuse liability, drugs that displace more [^{11}C]-raclopride binding (by producing higher increases in synaptic dopamine) should be more often abused by humans. In fact, finding a metric by which abuse liability can be assessed is an interesting and unresolved issue [13].

One way to define abuse liability is to identify the percentage of the drug-experimenting population who become dependent on a given substance. For example, according to a 1999 Institute of Medicine report, 32% of adult individuals who try tobacco become dependent, as do 17% of those who try cocaine, 11% of those who try other stimulants, 15% of those who try alcohol, 5% of those who try psychedelics and 4% of those who try inhalants. In Figure 3, these data are plotted on the ordinate axis, with the dopamine-induced change [^{11}C]-raclopride binding produced by that drug on the abscissa (from Table 1 and references therein).

Several caveats must be considered that limit the interpretation of this data: first, the route of administration is critical to drug-induced euphoria and to dopamine release, and in the survey data there were no specifications as to the route of administration of any of the drugs, whereas tobacco-induced changes in [^{11}C]-raclopride binding were measured from subjects who were actively smoking and who had abstained before the PET scan.

Figure 4 provides valuable information about the nature of addiction in humans. First, tobacco-induced increases in dopamine (or decreases in [^{11}C]-raclopride binding) were measured in smokers who were smoking at the time and who had abstained for a period of time (up to one day) before the experiment. All the smokers who had increases in dopamine reported euphoric effects from smoking. Perhaps if identical PET experiments were performed in addicts actively craving cocaine or methamphetamine the dopamine-induced change in [^{11}C]-raclopride binding would be greater than, for example, nicotine or alcohol. This is in contrast to animal PET experiments, where intravenous nicotine administration decreases [^{11}C]-raclopride binding by only 12% [14,15], and produces much smaller increases in extracellular dopamine compared with cocaine or amphetamine [14]. It is possible that this discrepancy between human behavior and animal models reflects two things: one, the role of the route of administration in the subjective euphoria associated with drug reward (animal models do not involve smoking cigarettes); and two, the societal impact of availability.

These PET data can be used to identify potential brain targets for the most optimal pharmacotherapy of a particular addiction (Figure 4). For example, drugs in development to reduce reward-induced changes in dopamine transmission (Table 2) might be more successful for the pharmacotherapy of psychostimulant use than for heroin or anxiolytic addiction.

Using PET to develop a treatment for substance abuse

The quantitative capabilities intrinsic to PET make it a suitable experimental tool for measuring the neuroanatomical distribution of specific receptors and their subtypes and the dynamic properties of these receptors along with their intrinsic ability to modulate other functionally-linked neurotransmitters. This strategy has evolved from pre-clinical primate PET experiments into a successful pharmacologic treatment for the management of cocaine and/or methamphetamine dependence [16].

Imaging neurochemical interactions with PET

Earlier studies that measured receptor density in drug-abusing or addicted patients did not address a possible multi-transmitter etiology for addiction. It can be assumed that changes in large numbers of individual neurons and very large numbers of synapses are involved in adaptive processes. This phenomenon is generally referred to as neural plasticity. Chronic exposure to drugs of abuse induces neural plasticity, and this most likely underlies the progression from experimental drug use to drug abuse and addiction. Therefore, the investigation of single receptor classes or locations in diseases such as addiction may lead to inconsistent results due to this complexity.

TABLE 1

Imaging studies involving drugs of abuse that have been conducted using PET

Compound of abuse	Radiolabeled compound of abuse	Metabolism and flow	Other radiotracers
Cocaine (coc)	The efficacy of [^{11}C]-coc to block DAT relates to the route of administration, closely associated with abuse liability [78]. Detoxified abusers showed decreased uptake of [^{11}C]-coc binding but no change in DAT [11].	When tested within 1 week of last coc use, coc abusers had significantly higher LMRGlu in the OFC and BG relative to controls or abusers 1 month after detoxification [11]. In polydrug abusers, IV coc decreased LMRGlu in cortical and subcortical structures [79].	Coc-induced increases in DA decrease [^{11}C]-rac by 25–30% [80]. This was blunted in coc addicts due to reduced DA synthesis, measured with [^{18}F]-FDOPA[81]. Coc-dependent men had increased [^{11}C]-carfentanil binding to μ-opioid receptors [82].
Nicotine (nic)	[^{11}C]-nic has shown that persistent reductions in binding after nic are from receptor occupancy by nornicotine [83]	TD nic increased LMRGlu in patients with Alzheimers, but not controls. In response to SC nic, increased LMRGlu in the thalamus and visual system of rats, consistent with dense nic receptors in these areas [84].	In dependent humans, smoking increases DA and reduces [^{11}C]-rac by 40%. This agrees with reduced levels of [^{11}C]-clorgyline and [^{11}C]-deprenyl in smokers. In animals, IV nic increases DA and decreases [^{11}C]-rac by 12% [14,15].
Alcohol (EtOH)	Pharmacokinetic PET studies in primates demonstrated that the distribution of [^{11}C]-ethanol resembled radiotracers that measure blood flow, like [^{15}O]-water and [^{15}O]-butanol [85].	EtOH decreased whole-brain metabolism more in male (-25%) than in female (-14%) subjects [86].	In healthy controls, EtOH increased DA and decreased [^{11}C]-rac by 14% [87]. [^{11}C]-flumazenil binding to BDZ receptors was lower in alcoholics.
Methamphetamine (meth)	In animals, meth sensitization and anesthesia alter the intensity and duration of brain [^{11}C]-meth uptake [88].	LMRGlu in meth abusers evaluated after short or protracted abstinence showed that the latter may reverse some meth-induced alterations in LMRGlu, but decreases in BG metabolism reflect long-lasting changes in DA cell activity [89].	In primates, meth-induced increases in DA cause 18–34% reductions in [^{11}C]-rac [90]. Chronic meth abuse reduces DAT density and D_2R [91].
Amphetamine (amp)	Studies using [^{11}C]-amp or [^{18}F]-amp show blood flow, lipophilicity and other transport mechanisms interfere with binding and make poor ligands [92].	Amp produced mania which correlated positively with LMRGlu changes seen in the PFC and BG [93].	Amp-induced increases in DA release decrease [^{11}C]-rac by 16%, which correlates with subjective ratings of euphoria [94].
Marijuana (THC)	The biodistribution of THC analogs in primates (-)-5′-[^{18}F]- Δ^8-THC included uptake in the BG, THAL and CB [95].	THC increased CB LMRGlu in naïve and chronic abusers, but only the latter increased LMRGlu in the OFC, PFC and BG [96]. CB LMRGlu correlated with the subjective sense of intoxication [97].	There have been no PET studies of the effects of THC on DA-induced changes in [^{11}C]-rac, and the interaction of THC with the reward system is not well understood at this point. In rodents, THC enhances DA, an effect bocked by opioid antagonists [98].
Phencyclidine (PCP)	The most promising PCP-analog radiotracer is [^{3}H]CNS-5161 [99]. Humans show a correlation between [^{11}C]CNS-5161 binding and memory changes, which opens the field for correlating addictive behaviors with glutamate function [100].	Acute PCP increases LMRGlu in PFC and BG. In PCP abusers, there was decreased LMRGlu in PFC, BG and THAL [101].	In humans the PCP analog, ketamine ('Special K'), decreased [^{11}C]-raclopride binding by 13.7% [19] or 0.7% [102].
Toluene (tol)	PET studies of [^{11}C]-tol in primates show significant uptake in the striatum, thalamus and frontal brain regions [103].	Decreases in CBF and LMRGlu were observed in PFC and CB of refinery workers exposed to solvents [104].	Tol-induced increases in DA decreased [^{11}C]-rac by 22% in rats [45], but there is no change in [^{11}C]-rac or [^{18}F]-DOPA in humans exposed to tol [105].
Opioids	[^{11}C]-carfentanil binds to μ-opiate receptors. Heroin abusers had more [^{11}C]-carfentanil in the PFC, and buprenorphine dose dependently blocked this binding. [^{11}C]-diprenorphine binds to all opiate receptor subtypes and may assess methodone efficacy in the treatment of opioid dependence [106].	Acute morphine in polydrug abusers reduced LMRGlu. A comparison of abstinent heroin abusers showed LMRGlu abnormalities several years after detoxification from methadone [107].	Heroin and related opiate agonists increase [^{11}C]-rac, consistent with a decrease in DA [108,109]. However, this is not consistent with evidence that opioid dependent subjects had lower D_2R relative to controls[110].
Benzodiazepines (BDZ)	[^{11}C]-flumazenil is an established BDZ radiotracer for PET[111]. Twice the usual hypnotic dose of zolpidem occupies only 25 – 30% of BDZ receptors [112].	BDZ-indiced decreases in LMRGlu in the THAL may explain its sedation, since these decreases correlated with sleepiness[113]. Decreases in CBF produced by lorazapam were antagonized by flumazenil [114].	Lorazepam either increased [18] or did not change [115] [^{11}C]-rac in primates and humans. Thus, it either increases or does not affect DA.

[^{11}C]-coc = [^{11}C]-cocaine; [^{11}C]-rac = [^{11}C]-raclopride; BDZ = benzodiazepine; CB = cerebellum; CBF = cerebral blood flow; coc = cocaine; DAT = dopamine transporter; LMRGlu = local metabolic rate of glucose; OFC = orbitofrontal cortex; IV = intravenous; SC = subcutaneous

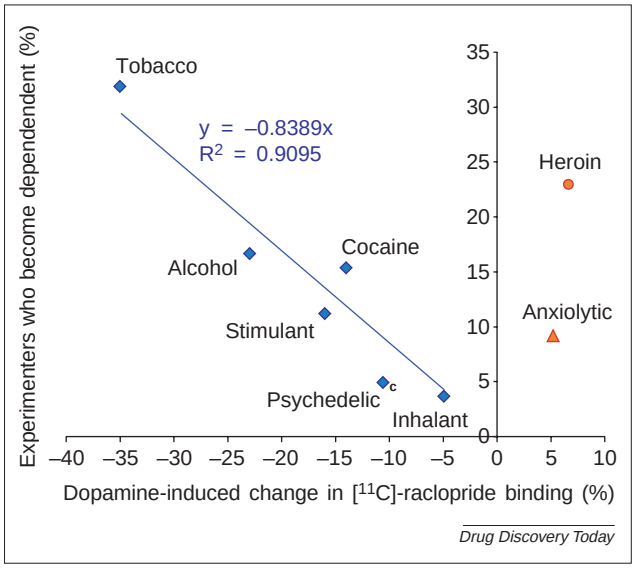


FIGURE 3

Does the change in dopamine correlate with abuse liability?
Human PET studies provide evidence that the abuse liability of some addictive drugs is associated with commensurate increases in dopamine levels (measured by the displacement of [^{11}C]-raclopride). Based on the inverse relationship between increases in dopamine and decreases in [^{11}C]-raclopride binding. The relationship between the percentage of drug-users who try a drug and become dependent on it (ordinate)[a] with the ability of that drug to increase dopamine release in humans (abscissa)[b] is reflected by a Pearson Correlation Coefficient (R^2), where 1.0 = perfect correlation.
[a]Data based on the National Comorbidity Survey of 8,098 persons aged 15-54 years old from the United States in 1991. Routes of administration not specified, nor was the specific type of drug within each class. Heroin and anxiolytics were not included in the correlation coefficient. [b]PET data represent the average values obtained from references cited for each drug listed in Table 1. Of note: Tobacco-induced changes in [^{11}C]-raclopride binding were obtained from subjects as they actively smoked following a period of abstinence. [c]Psychedelic drugs include two experiments which measured ketamine-induced changes in [^{11}C]-raclopride binding (Table 1) and an additional experiment that measured psylocibin-induced changes in [^{11}C]-raclopride binding [75].

Neuropsychiatric and neurodegenerative diseases have classically been attributed to deficits within a single neurotransmitter system. For example, dopamine might be a common denominator underlying the rewarding effects of several abused drugs. However, it is likely that the progression from experimental or acute drug use to chronic drug abuse alters the ability of dopamine to modulate or be modulated by other, functionally related, neurotransmitters. PET can be used to assess the functional integrity of neurotransmitter systems and the multiple mechanisms of drug action. It can provide a more comprehensive understanding of the fundamental mechanisms used by the CNS to maintain control over many biological processes. In addition, it can test alternative hypotheses regarding the etiology and subsequent pharmacotherapy of drug addiction.

According to one such hypothesis, the initial rewarding effects of abused drugs are related to alterations in dopamine, but the development of drug dependence actually relates to the ability of dopamine to modulate, or be modulated by, other neurotransmitter systems. Indeed, PET experiments have shown functional interactions between dopamine and serotonergic [17], GABAergic [18], glutamatergic [19] and cholinergic [20] systems. These systems act in parallel to excite or inhibit the flow of dopamine through mesolimbic reward circuits. Data with available radiotracers (see Table 2) implicate many neurotransmitter systems in the pathophysiology associated with chronic drug abuse (reviewed in [21]). Thus, the neurochemical aberrations which underlie specific phases of the human abuse cycle can be identified and treatments targeted accordingly. For example, it is now clear that some people cannot stop taking drugs even when PET data indicate that their brain chemistry has been normalized after a period of abstinence [10]. Perhaps maintenance treatment of this phase of drug addiction requires alternate pharmaco/behavioral therapies targeting a different neurochemical system from that which underlies the reinforcing properties of the drug itself.

Translational neuroimaging

PET has been widely used to characterize adaptations that occur with addiction and to guide new treatment strategies designed to interfere with the chemical effects of drugs on the brain. Because animal experiments play a critical role in our understanding of the neurobiology of addiction, the ability to image animals with PET has been one of the hallmark advances in neuroimaging. In this, PET offers a unique bridge between the contributions of animal experiments to drug research and development and the clinical pharmacotherapy of human addicts. For example, Figure 4 depicts the shared properties of [^{11}C]-cocaine from rodents through primates and finally in humans. Small-animal PET experiments provide an identical outcome measure as human PET experiments, but this burgeoning field has yet to establish whether animal brain activity parallels human brain activity to the same degree that animal models of addiction appear to correspond to human behaviors. Even more exciting, the use of repeated or serial PET scans in animals provides the unique opportunity to monitor these changes in brain activation coincident with the hallmark behavioral changes associated with animal models of drug craving and reward. This burgeoning field also has the potential to assess changes in gene expression associated with chronic drug abuse [22], or protection afforded by potential treatments [23], as well as phenotypic changes associated with targeted gene disruptions.

The efficacy of a potential treatment can be assessed in terms of its ability to curb animal behavior and its neurochemical impact on central reward systems. The observation that chronic drug abuse produces changes in the dynamics of the dopamine system has led to the development of many strategies targeting this system [24]. It is likely that some effective pharmacotherapies might not act on dopaminergic systems directly, but on the systems that modulate it.

Controlling dopamine stimulation to control addiction

Dopaminergic homeostasis is primarily maintained by the activity of excitatory amino acid (EAA) and inhibitory GABAergic systems [25]. Under the hypothesis that either *a priori* diminishing EAA neurochemical stimulation of dopamine or augmenting inhibitory GABAergic control will reduce the reward-associated response to a drug challenge, the potential of using these agents as therapies for drug abuse have been examined. Studies targeting EAAs support the notion that diminishing excitation of dopaminergic systems will reduce the stimulatory response to abused drugs. However, although rodent and primate studies suggest that antagonizing EAA glutamate receptors directly could reduce the dopaminergic response to drugs of abuse [26], conventional glutamate receptor antagonists are known to produce psychosis [27] and are self-administered [28]. Newer, non-competitive NMDA antagonist drugs, for example, amantadine or memantine, do not appear to have these negative qualities, but have shown limited success in human clinical trials [29]. Recent studies have shown that the dopaminergic properties of phencyclidine (PCP) can be inhibited by prior treatment with a GABA agonist, γ-vinyl GABA [30]. Thus, the GABAergic system might provide a more favorable approach to indirectly modulating the dopaminergic response to drugs of abuse.

Enhancing inhibitory control over dopamine to control addiction

Different mechanisms used to increase GABA and decrease dopamine each suffer trade-offs to the extent that none has proven particularly successful in human patients. Many of these compounds are currently approved by the FDA for use as anticonvulsant drugs, designed to curb the aberrant firing of neurons associated with seizures [31]. These compounds are also widely used to treat seizure activity secondary to cocaine overdose [32]. Ideally, a drug with a rapid onset of action and long duration would provide immediate relief for the craving addict in search of recovery, with minimal daily dosing schedules to adhere to. However, GABA agonists with a rapid onset of action are usually associated with a short duration, such that drugs that act quickly to produce an effect in the brain usually do not act for very long. On the other hand, drugs with an optimal duration of action usually require several weeks to produce their desired effect.

Augmenting GABA transmission as a strategy to treat drug abuse has been mainly assessed using drugs with one of three mechanisms. Drugs including tiagabine or NNC-711, which block GABA re-uptake, have a rapid onset of action, but are also short acting. Stimulating the activity of post-synaptic $GABA_B$ receptors with drugs such as baclofen has been the most widely tested GABAergic approach in humans to date, but the results remain inconclusive. Baclofen's duration of action is also short, so many daily doses are required to treat cocaine abuse. Mechanisms such as irreversible inhibition of the enzyme GABA-transaminase (GABA-T), responsible for GABA catabolism, for example, vigabatrin (GVG, γ-vinyl GABA), provide a long-acting duration of action, since the effects of GVG are reversed only by the *de novo* synthesis of GABA-T. This long duration of action is especially desirable from the pharmacotherapeutic perspective of preventing acquisition or relapse to previously acquired addictions, as daily treatment is probably not necessary.

An indirect mechanism also serves several mechanistic benefits. First, it reduces the potential for pharmacological tolerance within GABAergic systems [33]. Second, indirect mechanisms create a neurochemical milieu in which subchronic treatment with lower doses of vigabatrin might be more effective than higher doses [34]. It is critical to note that this only applies to subchronic or chronic treatment regimens because cumulative exposure is more important than it is with receptor-mediated mechanisms. Microdialysis investigations have shown that increases in GABA produced by this mechanism of action are highly reproducible and directly related to the degree of inhibition of GABA-T [35]. Nevertheless, no measured relationship between biochemical markers of GABA activity (i.e. GABA-T or GABA) and clinical seizure protection has been established [36]. Thus, measurements of neuron impulse dependency (like microdialysis and voltammetry) might provide misleading results. For this reason and others, downstream indices of dynamic GABA function might provide a more accurate index of its pharmacologic potential in the treatment of substance abuse.

PET studies provided evidence that GVG reduces the dopaminergic response to alcohol [37], methamphetamine [37], cocaine [38], nicotine [39] and PCP [14] in rodents and non-human primates. Concomitantly, GVG reduces the effects of cocaine-induced sensitization [40], brain reward stimulation [41] and cocaine self-administration

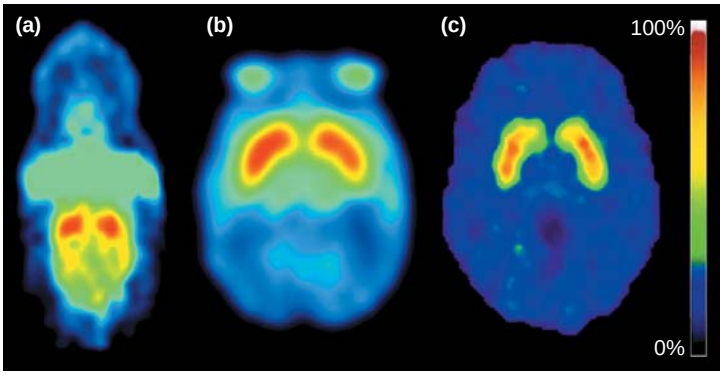
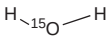
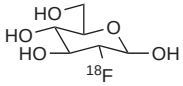
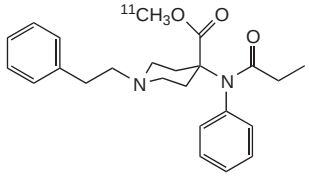
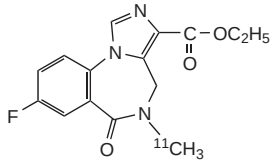
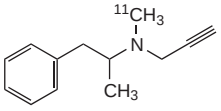
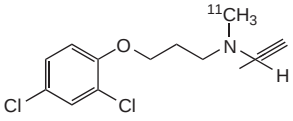
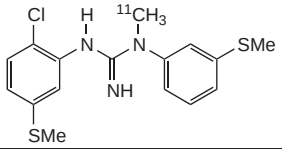
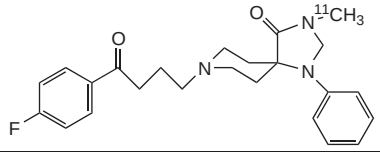
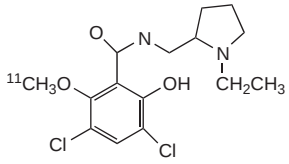
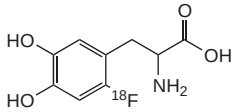
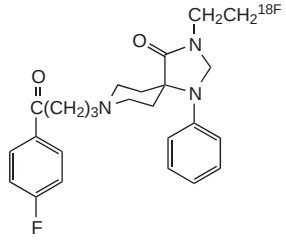
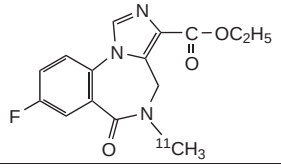


FIGURE 4

Translational neuroimaging. PET captures the radioactivity distribution of [11C]-cocaine from the rodent brain **(a)**, the non-human primate brain **(b)** and the human brain **(c)**. Rodent PET data was obtained from a microPET R4 scanner, the primate image from an ECAT HR+ and the human image was obtained from a CTI 931 tomograph. Radioactivity distribution images are colored using the extended rainbow color scale (far right) where red and white represent the image pixels with the highest radioactivity values.

TABLE 2

Radiotracers commonly employed to study brain function with PET

Radiotracer	Structure	Brain target/mechanism
[^{15}O]-Water		Radiolabeled water and carbon dioxide have both been used to study local cerebral blood flow.
2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG)		As an analog of glucose, ^{18}FDG is taken up by tissue as glucose but the [^{18}F]-label prevents further metabolism, trapping it as [^{18}F]-glucose-6-phosphate.
[^{11}C]-Carfentanil		[^{11}C]-Carfentanil is a μ-opiate receptor agonist that used to study opiate receptors and endorphin (the chemical natural ligand) in the brain.
[^{11}C]-Cocaine		[^{11}C]-cocaine has been used to study the distribution and pharmokinetics of cocaine and monoamine transporter proteins. Its time course in the striatum parallels cocaine-induced euphoria.
[^{11}C]-L-Deprenyl		Deprenyl (or Selegiline) antagonizes monoamine oxidase B (MAO-B), the enzyme that catabolizes dopamine.
[^{11}C]-Clorgyline		Clorgyline antagonizes MAO-A, an enzyme that catabolizes dopamine. [^{11}C]-Clorgyline has been monitored in the human brain and body by PET.
[^{11}C]-CNS-5161		To date, this is the most promising ligand for NMDA glutamate receptors. First tritiated (^{3}H) in 2001, it has recently been labeled with [^{11}C] and tested in humans.
[^{11}C]-N-methylspiperone ([^{11}C]-NMSP)		N-methylspiperone (NMSP) binds to dopaminergic D_2 receptors. [^{11}C]-N-methylspiperone has been used to study the neurochemical effects of various substances on dopaminergic function.
[^{11}C]-Raclopride		[^{11}C]-raclopride is used in PET to study the function of dopaminergic synapses. Raclopride binds to dopamine D_2 receptors and is a selective, reversible inhibitor of dopaminergic D_2 receptor function.
[^{18}F]-Dihydroxyphenylalanine ([^{18}F]-DOPA)		[^{18}F]-FDOPA can be used to examine the presynaptic distribution of stored dopamine. [^{18}F]-FDOPA uptake is related to the rate of production of dopamine.
[^{18}F]-Fluoroethylspiperone ([^{18}F]-FESP)		[^{18}F]-FESP is a radioligand used to probe dopamine D_2 receptors. [^{18}F]-FESP binds to D_2 receptors with high affinity; up to 10 times higher than [^{11}C]-raclopride, for example.
[^{11}C]-Flumazenil		[^{11}C]-flumazenil is a ligand for benzodiazepine receptors that is sensitive to changes in endogenous GABA, and widely used to measure pathological changes in both receptor and transmitter.

[42], without affecting the reward associated with food [42] or water [43] intake. In addition, GVG reduces indices of craving and drug-seeking behavior to cocaine [38], nicotine [39], heroin [44] or inhaled toluene [45], as assessed by the CPP paradigm.

Despite extensive and promising pre-clinical data with GVG for the treatment of addiction and despite its acceptance into mainstream clinical practice in over 65 countries worldwide [46], one potential side effect continues to cause concern. Asymptomatic concentric visual field defects (VFD) in patients taking GVG for extended periods of time were first reported in 1997 [47], nearly a decade after it was released for the treatment of partial complex seizures. Sufficient evidence has now accumulated to convince all but the most skeptical that GVG has a strong tendency to produce VFDs. It is not clear whether this effect is limited to GVG. Of all the antiepileptic drugs tiagabine is closest to GVG in its mode of action, because tiagabine blocks the reuptake of GABA at the synapse, thus increasing its availability, an effect that vigabatrin achieves by reducing its breakdown. If retinal toxicity were a class effect of drugs increasing the effect of GABA at retinal synapses, then tiagabine would appear the most likely candidate to exert a similar effect. In an abstract by Beran and colleagues, VFDs similar to those associated with vigabatrin were reported in 6 of 12 patients exposed to tiagabine [48]. Becaue GVG has primarily been used as adjuvant therapy, it is also difficult to accurately determine if the observed VFD is due to GVG alone, to the combination of GVG with other therapeutic drugs, or to damage resulting from a preexisting condition. Recent studies of GVG monotherapy have demonstrated the occurrence of an abnormal contrast sensitivity associated with VFDs in epilepsy patients, but not in healthy volunteers [49].

Evidence has been obtained indicating that patients can fall into the increased-risk category of VFDs after a non-interrupted treatment regimen ranging from 30–60 months at a daily dose of 1–6 g grams [50]. As a result, it now appears that a known lifetime cumulative GVG dose can be defined as an indicator of increased risk, which could be used to assess vulnerability to VFDs [51]. Whereas the knowledge of GVG doses required for seizure protection is crucial to our understanding of the biochemical mechanisms underlying this behavior, extrapolation of the epilepsy dose to an effective dose for the treatment of substance abuse must be made with caution. A fundamental tenet of addiction pharmacotherapy research should be that the etiology and subsequent progression of addictive processes differs markedly from that underlying seizure activity in epileptic patients. For these reasons, it is essential to establish a treatment regimen that adheres to the mechanisms associated with drug dependence. To that end, open-label clinical trials have demonstrated that it is possible to establish such a treatment strategy that would require little or no maintenance pharmacotherapy, while simultaneously preventing the induction of mechanisms associated with craving and relapse to methamphetamine and/or cocaine addiction [52]. With this information, the risk of VFDs in GVG-treated drug-dependent individuals can be reduced.

It seems unlikely that the emergence of serious, asymptomatic or even symptomatic VFDs will impact vigabatrin for the treatment of cocaine addiction, given the short duration of treatment that, at least preliminarily, seems effective. As a component of the second clinical trial using GVG for the treatment of cocaine and/or methamphetamine addiction, extensive visual field testing was conducted before, during and after completion of the drug protocol. No subject, regardless of whether they completed the trial, developed any visual field changes [53]. This provides evidence that at a cumulative dose of 137 g, less than 10% of the lifetime exposure where there appears to be an increase in the incidence of visual field abnormalities [50], GVG is safe. Further, no subject, whether they were drug-free or actively using cocaine or methamphetamine while on GVG, developed any changes in vital signs. Thus, based on this small, open-label clinical trial [52], GVG is safe for the treatment of cocaine and/or methamphetamine addiction.

PET studies provide support for GVGs 'use-dependent' mechanism

The ability of GVG to increase cytosolic pools of GABA [54] might contribute to its promise as a therapy for addiction. Ideally, future avenues would include a drug where the dopamine necessary for healthy locomotor activity and naturally rewarding events is spared, while the surge in dopamine released by psychostimulants is suppressed. In this way, the impact of the therapy depends on the magnitude of dopamine stimulation, or activity. GABA is one of a handful of neurotransmitter systems devoid of extracellular metabolizing enzymes. Instead, its action in the synapse is terminated either by diffusion to neighboring synapses, or by re-uptake through the GABA transporter [55]. GABA that has been taken back to the presynaptic cell is either degraded by GABA-T in the intracellular compartment, or cytosol, or packaged into synaptic vesicles (Figure 1). This scenario creates two distinct transmitter pools, vesicular GABA and cytosolic GABA [56]. Vesicular GABA is safe from the catabolic activity of GABA-T and is released with very strong stimuli through a Ca^{2+}-dependent mechanism [57]. Cytosolic GABA is generated from GABA re-uptake through transporters, and this pool is actively degraded by GABA-T. Release from this pool is driven by a concentration gradient that equilibrates intracellular with extracellular GABA [55]. This concentration gradient is maintained by the GABA transporter, which can either move GABA from the synapse into the cytosol (re-uptake) or reverse its direction and pump cytosolic pools of GABA out of the cell accordingly [for a review, see ref. 55].

Although this capacity of the GABA transporter has been known for some time, traditional models of synaptic

function accommodated it as a rare response to excessive stimulation or a pathological surplus of intracellular GABA [58]. In fact, recent studies suggest that vesicular GABA release is a rarity, and the majority of brain inhibition is governed by GABA-transporter reversal [55]. Thus, a significant portion of pre-synaptic GABA is sequestered in vesicular compartments that do not directly participate in the maintenance of basal arousal, but provide a braking mechanism in response to excessive stimulation. In this case, increases in specific intracellular pools of GABA are only released in response to abnormal stimulation of functionally related (dopaminergic) systems [59]. Clinical support for GVGs activity-dependence comes from PET studies using ^{18}FDG in epileptic patients to show that normal alterations in glucose produced by increasing GABA concentrations are only evident during seizure suppression in GVG-treated patients [60]. This hypothesis is further supported by pre-clinical evidence showing that GVG does not diminish locomotor activity at clinically relevant doses [43].

Facilitating compliance is fundamental to success

Targeting the dopamine system with GABA agonists or glutamate antagonists could produce secondary effects that are sufficiently unpleasant to reduce patient compliance. These effects are directly associated with suppressing the central mesolimbic reward system. Given the close relationship between the mesolimbic dopamine and locomotor activity, many drugs that appear to reduce the locomotor-activating properties of drugs of abuse merely inhibit the basal ganglia and other systems related to movement. Reducing dopamine transmission could also exacerbate symptoms of drug withdrawal, especially with alcohol or opiates.

In summary, drugs that depress dopaminergic function usually produce concomitant reductions in locomotor behavior [61]. Not only does this have implications for possibly reducing patient compliance, it also impacts the interpretation of results from animal models of drug abuse because animals need locomotor activity to indicate that they are addicted to a given compound (i.e. pressing a lever). Thus, the interpretation of reductions in drug-dependent behaviors should be viewed carefully because behavioral responses could reflect non-specific factors such as sedation or motor impairment, rather than specific reductions in the reinforcing properties of an abused drug. For example, some GABA agonists that reduce dopamine activity and self-administration of psychostimulants [62], do not affect the subjective euphoria of cocaine in humans [63] or animal models [64]. At high doses, baclofen reduces locomotor activity and response rates in some operant tasks [65]. Thus, by diminishing global motor activity, some GABA agonists diminish the ability to physically press the lever [64].

Complete antagonism of this central reward system might also antagonize rewards arising from naturally appetitive events. The impact of potential pharmacotherapies on naturally rewarding events can be assessed by food self-administration, a component of most pre-clinical self-administration experiments. Food-mediated response has been blocked by high doses of many compounds that directly or indirectly diminish dopamine transmission [42]. This is particularly relevant in drug-abusing populations, who through chronic stimulation of dopamine are most likely less-sensitive to the effects of naturally rewarding events.

Relatively little effort has been directed toward developing animal models of polydrug abuse, however, recent evidence suggests that it is possible to develop a successful model of oral cocaine/alcohol self-administration [43]. The ability of GVG to modulate simultaneous cocaine and alcohol intake increases the promise of this strategy to treat drug abuse [43].

Pharmacotherapies of the future

The main difference between the new pharmacological strategies for drug addiction and the older ones is the precision with which they target neurochemical brain processes, either by interfering with the mechanism of an abused compound (i.e. vaccines) or by interfering at an identified stage of the disease (i.e. D_1 receptor agonists or activity-dependent drugs).

Several drug candidates based on novel mechanisms of action are in development. Because dopamine (including noreprinephrine and serotonin) transporters are crucial in the rewarding and reinforcing effects of psychostimulants, these proteins are potentially fruitful targets for drug development. The 'tropane horse' strategy comprises a compound that binds covalently to the cocaine-binding site on the dopamine transporter. Upon binding, most of the molecule is cleaved from a small fragment which stays in the cocaine-binding site, preventing cocaine binding, but sparing free transport of dopamine [66]. This dopamine-sparing antagonist has the potential to surmount issues of non-compliance related to the lack of rewarding or reinforcing experiences.

Other dopaminergic strategies in development for the treatment of addiction include a dopamine D_1 receptor agonist and a dopamine D_3 receptor agonist. Imaging studies have shown that a lower concentration of D_1 receptors in the prefrontal cortex of patients with addictions, which might specifically target the decision-making processes thought to contribute to the development of substance dependence [67]. D_3 agonists have also shown promise in pre-clinical research and several partial D_3 receptor agonist–antagonist drugs have indicated that it is possible to reduce the motivation induced by a drug-related cue without interfering with the drug-related reward [68]. Currently, there are no PET radiotracers that have effectively isolated the D_3 receptor from the D_2 receptor.

Another promising approach is the use of vaccines or antibodies to prevent cocaine or nicotine from reaching their initial brain targets. For example, the natural

cocaine-metabolizing enzyme butyrylcholinesterase (or recombinant versions with enhanced capabilities), catalytic antibodies, or passive and active immunizations that make the body produce anti-cocaine- or anti-nicotine-binding antibodies [69]. For example, the antibodies can bind to a cocaine molecule in the bloodstream, before it reaches the brain, and facilitate a chemical reaction that destroys the molecule. A small amount of antibody would be required to inactivate a large quantity of cocaine before it enters the brain. A recent Phase I trial found the cocaine vaccine to be well tolerated and able to produce detectable levels of anti-cocaine antibodies for up to nine months after immunization [70]. Although no PET studies have been performed, there is potential to explore the transport of [^{11}C]-cocaine or [^{11}C]-nicotine into the brain in the presence of a vaccine. This approach could be used to assess the need for a cocaine vaccine booster.

Developing addiction therapies

PET and other imaging techniques have contributed greatly to our understanding of the underlying biology of addiction. These approaches are rapidly opening the door to the development of novel therapies, which are in great demand from a financial and public-health perspective. Any medication that is developed for the treatment of addiction might already be an effective medication for some other disorders. For example, we describe the activity dependence of GVG, which has successfully suppressed seizure activity in epileptics without a significant impact on the daily lives of those who take it. It is possible that this property could be mobilized for the treatment of stimulant-drug dependence only when a patient attempts to abuse stimulants, sparing naturally rewarding events. In turn, this might increase patient compliance and in combination with psychosocial rehabilitation, provide a successful treatment for stimulant dependence. The activity dependent approach is not unique to GVG either; several glutamate antagonists also appear to have activity-dependent properties *in vitro* [71]. Other drugs such as those listed in Supplementary Table S1 also have promise [71]. Alternatively, compounds that are developed to treat addiction might also be effective medications for other disorders. Drugs that target μ-opioid receptors can modulate stress and hormones as well as gastrointestinal and cardiovascular function, facilitating recovery from the damaging effects of stimulants on a holistic level [72].

However, the involvement of pharmaceutical companies in the development of pharmacotherapies for addiction has been limited for several reasons. One is stigma about potential patients as well as treatment providers. Another is the complex nature of the people who suffer from drug dependence; a notoriously unreliable patient population. These people would have to participate in clinical trials, presenting major problems from a medical and a legal stand point. High levels of co-morbidity and adverse events that could be attributed to a new medication, further reduce incentives for companies to become involved in this area. Further, drug dependence is a heterogeneous disease, with high likelihood for non-compliance accompanied by an unusually high placebo effect [73], greatly impacting the definition of treatment efficacy. This means that drugs that undergo clinical trials might be falsely ruled as inefficacious because they were tested in the wrong patient population, disease stage, or using inadequate efficacy end points. Pharmaceutical companies have been the leaders in drug development and their involvement in the search for a pharmacotherapeutic treatment for drug dependence is needed. Nevertheless, the seemingly poor reimbursement and financial pressures to hold down the price of addiction treatment are clear disincentives for companies to engage in developing addiction treatments.

These limitations are not without remedy. Addiction medicine is still in its infancy, and the stigma associated with the disease will dissipate as the clinical, biological and neurochemical forms are progressively identified and defined. When this complex, heterogeneous patient population can be treated according to these well-defined criteria, different stages of the disease process can be tailored appropriately. A long duration of drug action is desirable from the pharmacotherapeutic perspective of preventing acquisition or relapse, such that daily medication is not required. Psychosocial interventions and pharmacotherapeutic regimens using several medications separately or in combination should be used to target particular neurochemical pathways associated with active drug abuse, withdrawal or relapse. Treatment delivery, evaluation and outcomes should be equally specialized for each stage of the disease process. Given these solid end points, pharmaceutical companies can avoid considerable medical and legal hurdles, which in turn could reduce research and development costs. Whereas easing insurance restrictions might provide more financial incentive to pharmaceutical companies, there is also a misconception about poor insurance coverage of individuals with alcoholism or drug dependence – most are actually employed and have medical insurance [74]. Clearly developing targeted drugs for particular addictions, especially if they are divided first by the drug of abuse and then parsed into neurochemical or behavioral stage, is a riskier commercial proposition regardless of the status of insurance reimbursements. Either way, academics and industry need to collaborate in the service of defining clinical, biological, imaging and histological components of addiction. This will lead to clinically relevant animal models and surrogate markers of efficacy to guide early stage drug development.

Concluding comments

Human neuroimaging studies, in combination with extensive preclinical efforts, have unraveled much of the basic molecular biology of the rewarding effects of abused drugs. Together with the research knowledge from institutes like the National Institute on Drug Abuse (NIDA) and the

National Institute of Alcohol Abuse and Alcoholism (NIAAA), the underlying biochemical processes associated with addiction and its progression can now be associated with specific phases in the course of the disease. Indeed, these studies have shown far more clearly than before that addiction, like schizophrenia, depression, and dementia is associated with specific changes in brain organization and chemistry. That understanding has reached the point where it can be turned into action. The next few years should see an array of new treatments that will add up to a big change in the way drug addiction is viewed and dealt with by society.

The potential for PET, with its unique ability to monitor the biochemical activity of a given drug in the human brain, to play a significant role in the development of a treatment for addiction is becoming more evident. Advances in scanner technology have made PET and MRI translational approaches because small animals can now be viewed in the same light as humans. This will undoubtedly grant resolution to many debates about animal models of addiction, as well as expediting the development of successful, targeted therapies to treat the early and the late stages of drug dependence. That is, the hope for an effective treatment depends on our ability to maintain minds open to new ideas, mutual strategies and combined therapies in the service of helping our fellow man, even though he/she might be addicted to drugs.

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