OPINION

The dopamine theory of addiction: 40 years of highs and lows

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Abstract | For several decades, addiction has come to be viewed as a disorder of the dopamine neurotransmitter system; however, this view has not led to new treatments. In this Opinion article, we review the origins of the dopamine theory of addiction and discuss the ability of addictive drugs to elicit the release of dopamine in the human striatum. There is robust evidence that stimulants increase striatal dopamine levels and some evidence that alcohol may have such an effect, but little evidence, if any, that cannabis and opiates increase dopamine levels. Moreover, there is good evidence that striatal dopamine receptor availability and dopamine release are diminished in individuals with stimulant or alcohol dependence but not in individuals with opiate, nicotine or cannabis dependence. These observations have implications for understanding reward and treatment responses in various addictions.

Addiction is one of the biggest health problems facing the world today. Each year, many millions of people die as a result of addiction to substances such as tobacco and alcohol[1], and currently available treatments for addiction have limited efficacy and application. Thus, there is a great need to better understand the brain mechanisms that are involved in addiction so that new, better-targeted interventions can be developed.

A major breakthrough in brain research was made in the 1970s when the potential role of dopamine in addiction was discovered. This breakthrough stemmed from the finding of Olds and Milner[2] that rats would willingly and repeatedly self-stimulate particular areas in the brain with electricity, a process that the researchers called positive reinforcement. These areas were subsequently shown to comprise, in part, a set of dopamine neurons[3], which explained why drugs that enhanced the actions of this neurotransmitter (for example, stimulants) increased electrical self-stimulation[4]. A subsequent series of largely US-based studies revealed that blocking dopamine receptors with neuroleptic drugs impaired the reinforcing effects of stimulants in rats and primates. This research clearly placed dopamine as the central neurotransmitter in stimulant addiction[5] and suggested that it had roles in reward, motivation and incentive behaviour[6].

The next conceptual breakthrough came when a group of researchers in Sardinia, Italy, who pioneered the technique of brain microdialysis in rats, discovered that a range of other drugs of abuse (that is, not only stimulants) increased dopamine release in the nucleus accumbens, which is located in the ventral striatum[7]. This led to a general theory of addiction in which addictive drugs release dopamine but psychoactive, non-addictive drugs do not. The field developed rapidly from this point, with multiple replications of the early animal findings of dopamine being released by 'addictive' drugs and reported confirmations in humans using neurochemical imaging. These findings led to immense investment in research to alter dopamine neurotransmitter function as a route to treating addiction. Disappointingly, despite four decades of intense research effort, this theory has not led to new treatments. In this Opinion article, we chart the history of the dopamine theory of addiction, explore the current evidence for this theory and suggest that initial optimism must now be cautioned with a more objective view of the role of dopamine in addiction.

Dopamine and the drug high

Studying *in vivo* dopamine function in humans became possible in the mid-1990s with the development of radiotracer imaging techniques, such as ^{11}C-raclopride positron emission tomography (PET) and ^{123}I-iodobenzamide (IBZM) single-photon emission computed tomography (SPECT). These tracers can be used to measure the availability of striatal dopamine D2/3 receptors and changes in striatal dopamine levels in the synapse[8] (BOX 1).

The crucial breakthrough in imaging the human dopamine system in addiction came in 1994, when it was demonstrated that the combination of intravenous infusion of a central stimulant drug and SPECT or PET neurochemical imaging of dopamine D2/3 receptors could be used to indirectly measure dopamine release in the human striatum[9,10] (BOX 1). The magnitude of this increase was later shown to predict the euphoria[10], or 'high' (REF. 11), produced by the drug. This was interpreted as proving that the experience of pleasure (the rewarding action) of stimulant drugs in humans was mediated by striatal dopamine release, just as in rats[7]. This was a powerful message that many researchers sought to develop. A succession of other human studies followed, which showed that alcohol[12,13], tobacco[14], ketamine[15] and cannabis[16] increase striatal dopamine release in healthy participants and in non-dependent drug users, thereby providing support for the dopamine theory of addiction (FIG. 1).

The dopamine theory of addiction rapidly became accepted by the field, and drugs that induce dopamine release were consequently considered to pose a risk of abuse. An example of such a drug is modafinil, which is used to treat narcolepsy. A ^{11}C-raclopride dopamine imaging study found that modafinil produced an increase in dopamine release[17]. This finding was interpreted to mean that modafinil carries a potential risk for abuse, despite the increase in dopamine release not being associated

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Box 1 | **Imaging dopamine receptors and dopamine release**

Imaging dopamine in the human striatum

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are quantitative radioactive imaging techniques that can be used to measure the availability of receptors and transporters, as well as the release of neurotransmitters. In the case of the dopamine system, radiotracers such as ^{11}C-raclopride (for PET) and ^{123}I-iodobenzamide (for SPECT) can reliably measure the availability of the combination of dopamine D2 and D3 receptors (generally referred to as dopamine D2/3 receptors) in the human striatum, the brain area with the highest density of these receptors. This includes the ventral striatum (also known as the nucleus accumbens), which is the region of the striatum that seems to be particularly involved in the acquisition of drug addiction. Most D2/3 radiotracers, and in particular the ones with agonist properties, such as ^{11}C-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol (^{11}C-PHNO), also have the ability to compete with the brain's endogenous dopamine to bind to D2 and D3 receptors[125]. Increases in extracellular dopamine levels elicited by pharmacological challenges, such as with methylphenidate[9] or amphetamine[10], or non-pharmacological manipulations, such as stress, playing a video game or cue-induced drug craving[8], can be detected as a decrease in the radiotracer binding owing to increased competition for the striatal D2/3 receptors (reviewed in REF. 8).

Extra-striatal dopamine imaging

The development of radiotracers with higher affinities for D2 and D3 receptors — for example, ^{18}F-fallypride, (*S*)-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide (^{11}C-FLB 457)[126] and ^{11}C-PHNO[127] — has made it possible to image these receptors in brain regions outside the striatum (for example, in the frontal cortex), where the density of D2 and D3 receptors is lower. Radiotracers such as ^{11}C-propyl-norapomorphine and in particular ^{11}C-PHNO not only have high-affinity agonist properties but also have a higher affinity for dopamine D3 receptors over D2 receptors. This additional quality enables the quantification of D3 receptor availability and dopamine release in key areas of the brain in addiction, such as the globus pallidum, ventral tegmental area, amygdala and hypothalamus[128].

with an increase in 'liking' scores[17] and prior clinical evidence showing that modafinil did not cause reinforcing behaviour[18].

The dopamine theory of reward had a profound effect on the development of drugs that target the brain. Pharmaceutical companies routinely used rodent microdialysis assays of ventral striatal dopamine release to estimate the presumed abuse potential of new drugs, discarding compounds such as potential novel antidepressants if they increased dopamine levels (D.J.N., unpublished observations). This is particularly concerning given that the latest work using optogenetics to control dopamine neurons in mice shows that dopamine activity in the ventral striatum is vital in resilience against depression[19].

However, studies of alcohol[20], cannabis[21,22] and ketamine[23,24] showed that these abused substances do not inevitably induce dopamine release in humans. Moreover, unlike with stimulants, an association between striatal dopamine release and pleasurable or hedonic effects of these substances was less apparent. For instance, there was no relationship between increased striatal dopamine release and any behavioural, subjective or physiological effects of cannabis[16,21]. In the case of alcohol, impulsivity and intoxication, but not a drug high, were associated with increased dopamine levels[12,20].

Despite these inconsistencies and the fact that all of these drugs produced lower levels of dopamine release than intravenous administration of the stimulant methylphenidate, which is used to treat attention deficit hyperactivity disorder (ADHD), a prevailing view developed that that the dopamine system had a central role in addiction that was applicable to all addictive drugs. Dopamine became characterized as the 'pleasure' neurotransmitter in the human brain — that is, the one that produces reward[25–27]. This model of addiction even made the cover of *Time* magazine and is widely quoted as a fact in current textbooks and by Wikipedia (for example, see the Wikipedia entries for 'reward system' and 'dopamine').

From the beginning there were doubts about whether this theory applied to drugs other than stimulants and even whether dopamine release was central to the rewarding effects of stimulants in humans[28]. Studies in rats showed that dopamine receptor blockade did not dampen the rewarding actions of opiates (for example, see REF. 29), and subsequent clinical trials revealed that blocking dopamine receptors was generally ineffective in blocking the rewarding effects of stimulants in humans[28] or in treating human addiction (even stimulant addiction)[30]. Moreover, several studies found that opiate administration was not associated with striatal dopamine release in opiate dependence. For example, a study in individuals addicted to heroin revealed that an intravenous dose of 50 mg heroin had no effect on striatal dopamine levels, despite producing a pronounced euphoric high[31]. This finding was subsequently replicated in a study that further showed that expectation of a heroin reward (in the absence of actual heroin administration) was not associated with dopamine release[32].

Various studies of nicotine mostly suggest that this compound causes a small increase in ventral striatal dopamine levels. For example, smoking cigarettes has been shown to produce a 7% reduction in ^{11}C-raclopride PET binding (when compared with smoking nicotine-free cigarettes)[33], whereas amphetamine produces a 10–20% reduction in the binding of this ligand[34–42] (FIG. 1). However, another study (in a small cohort) found that intranasal nicotine administration had no effect on ventral striatal dopamine release[43]. This finding may be consistent with the idea that some of the effects of tobacco are due, in part, to the burning of tobacco-producing substances that block monoamine oxidase B — the enzyme that degrades dopamine[44].

Studies of Δ^9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, found that this compound had even smaller effects on striatal dopamine release than nicotine. Administration of oral THC was associated with a non-significant reduction of around 2.5% in ventral striatal ^{11}C-raclopride binding[21]; inhaled THC was linked with a significant reduction of around 3.5% in ventral striatal ^{11}C-raclopride binding[16]; and intravenous THC was associated with no significant change in ^{123}I-IBZM SPECT binding[22]. The changes in ^{11}C-raclopride reported in these studies[16,21,22] for THC were all less than the test–retest variability of the tracer[45], which means that it is possible that they are the result of normal variation in the PET signal rather than being produced by THC administration. Although THC administration produced marked behavioural effects — such as perceptual distortions, cognitive disorganization[21] and even psychotic symptoms[22] — in these studies, it seems that these cannot be satisfactorily explained by striatal dopamine release.

Lower dopamine function?

If the dopamine system is critically and universally involved in dependence to all drugs, we might expect changes in dopamine function to be apparent across all addictions. Two markers of abnormal dopamine function in drug dependence have emerged: the

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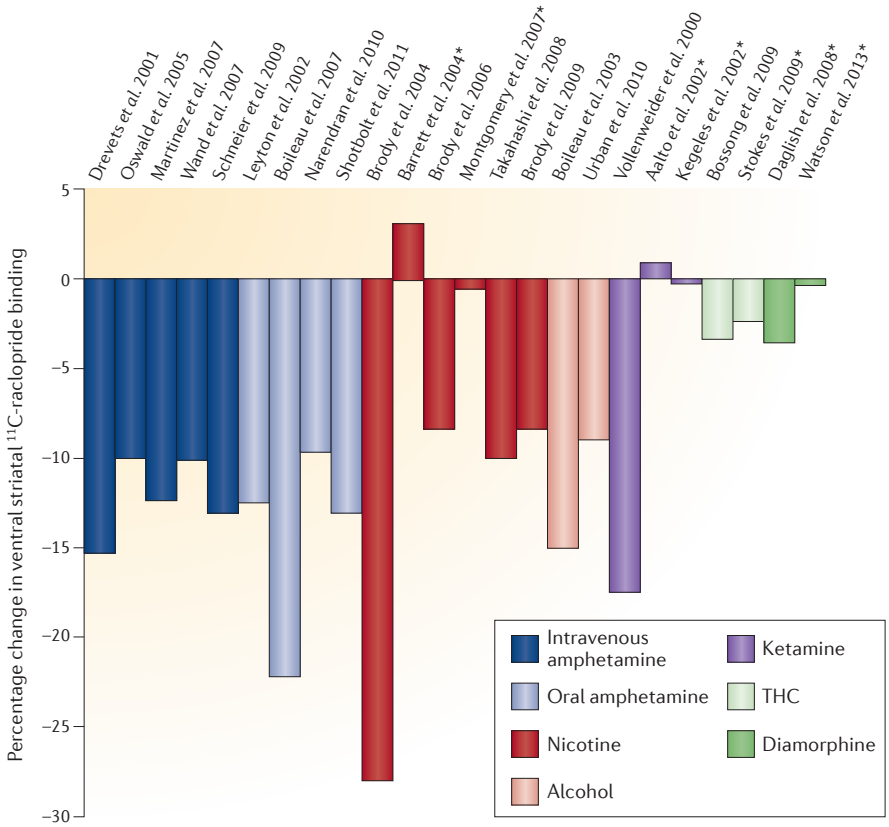

Figure 1 | **The effect of abused substances on human ventral striatal dopamine release.** These studies[12–16,21,23,24,31–43,129–131] used the dopamine D2 and D3 receptor positron emission tomography (PET) radiotracer ^{11}C-raclopride to investigate the effect of abused substances on dopamine release in the ventral striatum. Decreases in ^{11}C-raclopride PET binding occur as a consequence of increased competition between dopamine and the tracer, and so percentage decreases in ^{11}C-raclopride binding reflect increased synaptic ventral striatal dopamine levels. These studies show consistent significant increases in ventral striatal dopamine levels produced by amphetamine and alcohol administration, less-consistent increases produced by nicotine, and non-significant or small increases associated with ketamine, Δ^9-tetrahydrocannabinol (THC) or diamorphine administration. The data presented are derived from published studies describing changes in the ventral striatum because this striatal area is the most relevant one to the theory of reward and dopamine; some studies are therefore not represented because data were available only for the whole striatum. The studies contained in the figure are broadly comparable, although there is some variability in the number of participants imaged between studies and the statistical tests used (mostly *t*-tests). The asterisks denote studies in which the change in ^{11}C-raclopride binding was reported as non-significant.

lower availability of striatal dopamine receptors and the diminished release of striatal dopamine in response to a pharmacological challenge (so-called blunting).

Lower striatal dopamine receptor availability. Early radiotracer imaging studies revealed that cocaine users had lower striatal dopamine D2 and D3 receptor availability than matched controls[46]. This was attributed to the effects of cocaine: cocaine induces dopamine release, which could be expected to downregulate postsynaptic dopamine receptors, leading to reduced receptor availability. This result has since been replicated in further cohorts of cocaine[36,47–51] and methamphetamine[52–54] users. Moreover, at least in cocaine addiction, this reduction in receptor radiotracer binding has been shown to result from the decreased expression of postsynaptic dopamine D2/3 receptors rather than from higher synaptic dopamine concentrations that compete with the radiotracer[49] or from altered receptor affinity for dopamine[50]. Decreased dopamine receptor availability has also been reported in individuals who are alcohol-dependent[55–60] and, interestingly, higher striatal dopamine receptor availability may be protective against alcohol dependence in high-risk individuals (relatives of individuals with alcohol dependence)[61].

However, differences in striatal dopamine receptor availability have not been as convincingly demonstrated in other addictions. Three studies have reported that individuals with opiate addiction have lower striatal dopamine receptor availability than healthy participants[62–64], whereas we have found no change in receptor availability with opiate addiction[31]. In nicotine addiction, two related studies have reported lower striatal dopamine receptor availability in male but not female cigarette smokers[65,66], and three studies have found no differences in receptor availability between individuals who smoke and healthy non-smokers irrespective of gender[67–69]. There is no evidence of changes in striatal dopamine receptor availability in cannabis addiction[70–74], and we could not find any published studies on such changes in ecstasy or ketamine users.

The observation of lower striatal dopamine D2/3 receptor availability in drug dependence also presents something of a paradox. One might predict that if striatal dopamine release was pleasurable, then lower receptor availability would to lead to a reduction in this effect. However, seminal studies by Volkow and colleagues[75,76] found the opposite; namely, individuals with low striatal dopamine D2/3 receptor levels (as measured by ^{11}C-raclopride PET) reported more pleasurable effects from stimulants. Animal studies have also supported this finding. For example, in rats, low dopamine D2/3 receptor levels in the striatum are good indicators of more cocaine self-administration[77] but not of more heroin self-administration[78]; in monkeys, higher striatal D2/3 receptor levels are associated with lower cocaine intake[79]. In addition, increasing dopamine receptor levels (through viral vector-mediated expression of the receptors) in the ventral striatum of dependent rats reduces both cocaine[80] and alcohol[81] intake.

These findings present a challenge to the original theory that dopamine release is responsible the euphoric effect of abused substances. If dopamine acting through D2 and/or D3 receptors is necessary to experience a drug high, then lower receptor availability should result in less-rewarding rather than more-rewarding drug effects.

Blunted dopamine release in dependence. In many but not all addictions, individuals show a blunting of striatal dopamine release (that is, the release of striatal dopamine is decreased in these individuals compared with healthy individuals) after a pharmacological challenge with either the misused drug or a stimulant. This phenomenon was

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first reported in 1997 in participants with cocaine dependence after a methylphenidate challenge[82] and has been replicated several times in participants with stimulant dependence[36,51]. Decreased dopamine release has also been demonstrated in opiate dependence after a methylphenidate challenge[64] and in alcohol dependence after an amphetamine challenge[57,60] (FIG. 2). By contrast, no marked blunting of dopamine release was found in cannabis dependence after an amphetamine challenge[72].

Recent studies show that the extent of blunted striatal dopamine release in stimulant addiction may predict treatment response and vulnerability to addiction. In cocaine users, low levels of stimulant-induced dopamine release were associated with a preference for cocaine to money[36] and worse treatment outcomes[51]. An elegant study of young people at ultra-high familial risk of addiction who used stimulants occasionally but who were not yet dependent showed that amphetamine-induced dopamine release in these individuals was reduced compared with that in well-matched controls[83]. One interpretation of these data is that low levels of dopamine release indicate a vulnerability to addiction, thus turning the dopamine theory on its head; instead of being the cause of addiction, dopamine might, if anything, have a role in resilience against becoming dependent and may be crucial for recovery from addiction[51]. However, it is also possible that ultra-high-risk participants had not become addicted because they experienced lower levels of dopamine release.

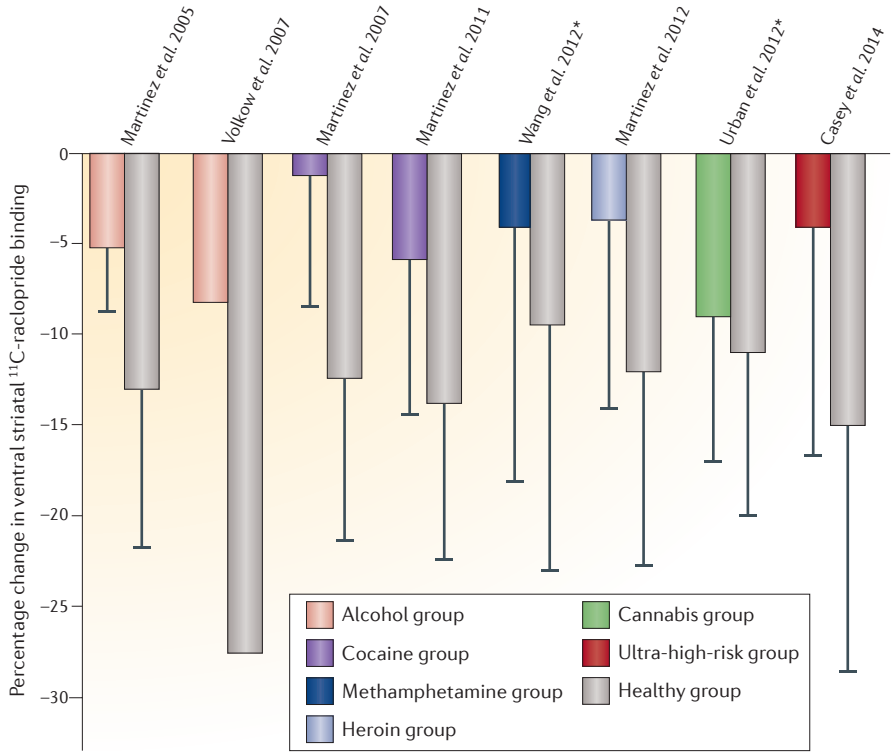

Figure 2 | **Investigating diminished ventral striatal dopamine release in addictions.** These studies[36,51,54,57,60,64,72,83] used the dopamine positron emission tomography (PET) radiotracer ^{11}C-raclopride to investigate whether diminished ('blunted') ventral striatal dopamine release occurs after administration of a stimulant (amphetamine or methylphenidate) in a range of substance addictions. Decreases in ^{11}C-raclopride PET binding occur as a consequence of increased competition between dopamine and the tracer, and percentage decreases in ^{11}C-raclopride binding therefore reflect increased synaptic ventral striatal dopamine levels. The studies contained in the figure demonstrate significantly diminished ventral striatal dopamine release in individuals dependent on alcohol, cocaine and heroin, as well as in individuals at ultra-high risk of developing addiction, but found no diminishment of release in cannabis or methamphetamine users. We selected studies that administered either amphetamine or methylphenidate because these directly target the dopamine system; therefore, any differences in dopamine levels reflect changes in this system. For each study, the percentage change in ^{11}C-raclopride binding is given for healthy participants and for the addicted population; the error bars show standard deviation. Volkow *et al.*[60] do not report standard deviation in change in ^{11}C-raclopride PET binding. The studies contained in the figure are broadly comparable, although there is some variability in the number of participants imaged between studies and the statistical tests used (mostly *t*-tests). The asterisk denotes a non-significant difference (according to the original study) in ^{11}C-raclopride binding between the healthy participants and addiction groups.

Addiction to the dopamine theory?

It is worth reflecting on why enthusiasm for the universal dopamine theory of addiction developed and then came to dominate the field of addiction research. There are several interacting factors. First, the animal dialysis studies were novel and compelling, and were seemingly confirmed by the beautiful studies of Schultz[84], which showed that dopamine neurons fired in response to rewards in monkeys. However, the relative discrepancies in the magnitude of dopamine release elicited by different drugs[7] should have given the field pause for thought. The stimulants produced striatal dopamine increases that were many-fold greater than those produced by the other, non-stimulant drugs, yet human experience suggests that stimulants are not more pleasurable or addictive[85]. Findings from studies investigating only stimulants (generally cocaine or amphetamine) were often discussed as though they applied to all addictions, even though there was no evidence for such an assumption[86]. Indeed, in studies that have been conducted using the same animal models, it is clear that stimulants differ from opioids, for example, in terms of the effects of low dopamine receptor number and drug self-administration[77,78].

Second, the methylphenidate experiment in humans showed such a clear relationship between dopamine release and the perceived high that it appeared mechanistic — the higher the level of dopamine release, the bigger the high[75]. However, what was overlooked was the fact that methylphenidate and other stimulants act specifically on the dopamine system to increase dopamine levels. Thus, dopamine must be the proximal mediator of any psychological response to stimulants, and it should not be surprising that the change in striatal dopamine release correlates with the subjective high. However, this is an association rather than a proof that the change in striatal dopamine levels mediates the high for stimulants. For other psychoactive substances that only indirectly act on dopamine neurons — such as alcohol and nicotine, which act by modulating dopaminergic neuronal firing in the ventral tegmental area — the association between changes in dopamine levels and high has been harder to show.

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Increased dopamine release has also been reported in rewarding activities such as playing computer games[87], practising meditation[88] and eating[89], and in the placebo response to L-3,4-dihydroxyphenylalanine (L-DOPA)[90]. These findings have been used to 'prove' the dopamine theory of addiction because they associate rewarding activities with dopamine release and thereby generalize the model to one that proposes all rewarding activities must be mediated by dopamine release. However, these studies imaged small numbers of participants and have rarely been replicated. The apparent rush to publish findings showing that any given pleasure-inducing drug or behaviour can induce dopamine release reflects one of the more worrying and pervasive aspects of science today — the preeminence given to reporting 'positive' data in support of currently influential theories. There is a concern that the classic Popperian approach to science — namely, refuting hypotheses — may be lost in the desire to publish papers that apparently prove the theory and are consequently well cited but often not replicated.

Does dopamine have other roles?

Dopamine has many roles in normal brain function. In the cortex, dopamine is important for executive functions such as attention and working memory[91]; in the basal ganglia it is necessary for motivational salience, reward and fluent motor function; and in the hypothalamus it regulates prolactin release. Furthermore, dopamine has been shown to have a major role in the pathogenesis of a proportion of cases of psychosis[92] and to be involved in positive mood in humans[93].

Changes in dopamine function in the basal ganglia can lead to compulsive-type behaviours. One theory of dopamine's involvement in stimulant addiction is that the initial pleasurable effects of these drugs are detected in the nucleus accumbens, and that with repeated use of the drugs, the drug-taking behaviour becomes encoded as habit in the caudate and putamen through progressive activation of the spiral of interacting striatal–cortical circuits[94,95].

As in rats, dopamine receptor availability in humans might relate to impulsivity (which itself is a risk factor for addiction)[96,97]. It has been proposed that low D2/3 receptor availability and low dopamine release in the striatum — as described in substance addiction, obesity and ADHD — are neurobiological markers of increased impulsivity[96]. The relationship between impulsivity and dopaminergic function has been investigated in another disorder with high levels of impulsivity: pathological gambling (that is, in individuals who are addicted to gambling). This disorder was recently re-categorized from an 'impulse control disorder' in the *Diagnostic and Statistical Manual of Mental Disorders: Volume IV* (DSM-IV) to a 'behavioural addiction' in DSM-5 owing to clinical and cognitive similarities with substance addiction. Thus, pathological or disordered gambling serves as a useful model for studying addiction in the absence of any drug-induced changes in neurotransmitter function[98].

In contrast to substance addiction, no differences in baseline D2/3 receptor availability have been found in pathological gamblers compared with healthy controls[99,100]. However, in one of these studies, striatal D2/3 receptor availability was inversely correlated with mood-related or 'rash' impulsiveness[100], and in the other, D2/3 receptor availability was positively correlated with impulsiveness in the substantia nigra, a dopamine D3 receptor-rich brain region[99]. Unlike the blunted stimulant-related dopamine release that is seen in substance addiction, dopamine release was increased in the dorsal striatum after amphetamine administration in pathological gamblers compared with healthy volunteers[101]. This increase in dorsal striatal dopamine was predicted by the availability of D3 receptors, and the authors of this study proposed that D3-related mechanisms might contribute to sensitization in this behavioural addiction[101]. The finding of increased stimulant-related dopamine release in pathological gamblers would also be consistent with the development of pathological gambling that is associated with dopamine replacement therapy in Parkinson disease (PD). Indeed, patients with PD who demonstrate impulsive–compulsive behaviours, such as pathological gambling, show increased ventral striatal dopamine release after the presentation of rewarding cues[102] in a similar way to cocaine users who show increased dorsal striatal dopamine release after the presentation of cocaine-related cues[103].

Therefore, depending on the disorder associated with impulsivity, either lower or higher dopaminergic function has been found. It may be that rather than a linear relationship, an inverted-U type of response function for dopamine underpins the relationship with impulsivity such that an increase or a decrease in dopamine levels may be required to improve inhibitory control; for example, an increase in dopamine levels may improve inhibitory control in ADHD, but a decrease in dopamine levels may improve such control in gambling associated with dopamine replacement in PD.

Dopamine may also have a role in regulating the motivation to seek drugs. The induction of craving is associated with cue-induced striatal dopamine release in cocaine users[103–105], although this is not the case in individuals addicted to heroin[32]. Dopamine has been proposed to have a role in motivation more generally[94], which could explain why, in stimulant users, it might both drive use and be necessary for recovery from addiction. Dopamine also has a role in executive function[106] (which includes inhibitory control) and, by acting through a top-down cortico–striatal mechanism, may have a role in preventing addiction and other dyscontrol disorders, such as overeating[107].

There is further evidence to support a possible protective role for dopamine in some drug users. A study in non-treatment-seeking stimulant-dependent individuals[108] showed that the dopamine D2 and D3 receptor agonist pramipexole had different effects on psychological performance in a Stroop task and related functional MRI measures in individuals with high drug-related compulsivity compared with individuals with low drug-related compulsivity. If this finding is replicated with cocaine and in people with other drug dependencies, it might lead to a more sophisticated view of dopamine in addiction and, potentially, to targeted interventions such as the use of dopamine-promoting agents in individuals with addiction who exhibit impulsivity. Moreover, the results of the pramipexole study[108] may provide an explanation for the partial efficacy of dopamine receptor agonists (such as bromocriptine[109]) and dopamine metabolism inhibitors (such as disulfiram[30]) in the treatment of alcohol and cocaine dependence, respectively.

Areas for future research into the relationship between human dopamine system and addictive drugs are outlined in BOX 2.

Limitations

Neurochemical imaging has led to crucial advances in our understanding of the role of the human dopamine system in addiction; however, there are limitations associated with the imaging technique and with the populations that have been imaged.

Current dopamine radiotracers bind to D2 and D3 receptors irrespective of their synaptic location. Moreover, with the exception of ^{11}C-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol (^{11}C-PHNO), which preferentially binds

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Box 2 | **Key issues and perspectives for future research**

To optimize our understanding about the relationship between the human dopamine system and addictive drugs, future research should consider several questions. First, who is being imaged? When selecting research participants, it is crucial to carefully describe factors that are likely to influence dopamine function, such as the lifetime use of alcohol and drugs, prior or current treatments, and periods of and current length of abstinence. Most individuals with a drug addiction use more than one substance and, other than tobacco smoking, such co-morbidity is usually an exclusion criterion for studies in addiction. Selection of a control group that matches potentially important confounders — such as intelligence quotient or years of education, family history, and alcohol, tobacco and other drug use — can be challenging.

Second, how is dopamine release induced? Stimulants are traditionally used in studies to increase dopamine levels. However, this pharmacological challenge may not be salient to individuals with addiction. For instance, many individuals with alcohol-use disorders do not find stimulants rewarding, so in these individuals, any changes in dopamine levels that are induced by stimulants reflect what is available for release but do not inform us about 'dopamine and reward'. Indeed, in such individuals, stimulant administration may be experienced as aversive. In some studies, addicted individuals were administered their 'drug-of-choice', but not in the way they would normally self-administer it (for example, nicotine inhalators versus smoking), thereby reducing the salience of the drug, which could affect dopamine responses. An inherent limitation of positron emission tomography protocols is that the drug-taking context cannot be simulated, but pharmacological and behavioural challenges should at least be optimized to reflect 'usual' drug behaviour.

Third, what is the role of cortical dopamine function? Most neurochemistry studies in addiction have imaged dopamine function in the human striatum. Such studies do not capture the importance of dopamine in mediating processes that are key to addiction, such as compulsion and executive functions, which are largely cortical. We suggest that an important step for future studies is to characterize cortical dopamine function in addictions, particularly because substantial advances in human cortical dopamine imaging have been made in the past decade.

to D3 receptors, these radiotracers bind with very similar affinities to D2 and D3 receptors. This means that for most studies it is difficult to assess whether differences in dopamine radiotracer binding between populations reflect altered D2 or D3 receptor availability. It also means that it is not possible to determine whether differences in binding reflect alterations in presynaptic or postsynaptic D2 or D3 receptors; however, because animal studies show that the majority of striatal dopamine D2 and D3 receptors are localized postsynaptically[110], most groups have interpreted differences as indicating changes in postsynaptic D2 and D3 receptors. The sensitivity of neurochemical imaging to lower levels of dopamine release produced by pharmacological challenges is also limited by the variability in the PET or SPECT imaging signal, so that changes of 5% or less in binding could be a result of lower levels of dopamine release or variability in the signal. This is an important limitation because a primate study has shown that, at least for the SPECT radiotracer ^{123}I-IBZM, which has a lower resolution than PET radiotracers such as ^{11}C-raclopride, a 1% decrease in binding equates to a 40% increase in dopamine release[111].

There are also limitations in the types of populations imaged; the large majority of studies have imaged dependent populations, and only a few (for example, REF. 83) have imaged those at high risk of developing addictions. This means that we do not know whether the changes in dopamine function reported in dependence are a consequence of substance use or are present before the onset of addiction and may mediate vulnerability.

The fact that there are only few dopamine neurochemical imaging studies available for most of the investigated substances, together with the fact that multiple methods have been used to define striatal regions (which is partly due to the gradual improvement of scanning techniques over the past few decades), means that conducting meta-analyses to synthesize findings across each addiction is challenging.

Conclusions

The dopamine theory of reward and addiction, which states that dopamine release mediates reward and thus leads to addiction, has had huge traction. However, it became accepted as a 'universal' theory without properly accounting for findings from studies in different drug addictions that did not support the theory. Tellingly, the dopamine theory has not led to any new treatments for addiction. We suggest that the role of dopamine in addiction is more complicated than the role proposed in the dopamine theory of reward. We propose that dopamine has a central role in addiction to stimulant drugs, which act directly via the dopamine system, but that it has a less important role, if any, in mediating addiction to other drugs, particularly opiates and cannabis.

Addiction is a complex mixture of behaviours and attitudes that vary from drug to drug and from user to user, and it is unlikely that a single neurotransmitter could explain every aspect of addiction. We foresee that addiction will be conceptualized as a multiple-neurotransmitter disorder in which the dopamine system is central to stimulant addiction but in which other neurotransmitter systems, such as the endogenous opiate or GABA systems, have important roles in other drug addictions. For example, endogenous opiates have been shown to be released by stimulants[112] and alcohol[113]; higher opiate receptor availability has been found in cocaine[114,115], opiate[116] and alcohol[117–119] dependency; and alcohol dependence and pathological gambling can, to some extent, be treated with opioid antagonists such as naltrexone[30] and nalmefene[120–122]. Moreover, individuals with alcohol dependence have lower limbic $GABA_A$ receptor availability[123], whereas individuals with a history of cigarette smoking have higher limbic $GABA_A$ receptor availability[124].

In conclusion, this account of the rise and fall of the universal dopamine theory of addiction serves as a lesson in neuroscience research. Unifying theories, although intrinsically appealing, should be subject to careful scrutiny just like other theories — and perhaps even more so because they can lead the field into directions that ultimately prove to be unfruitful.

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1. Wittchen, H. U. *et al.* The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur. Neuropsychopharmacol.* **21**, 655–679 (2011).
2. Olds, J. & Milner, P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* **47**, 419–427 (1954).
3. Crow, T. J. A map of the rat mesencephalon for electrical self-stimulation. *Brain Res.* **36**, 265–273 (1972).
4. Stein, L. Self-stimulation of the brain and the central stimulant action of amphetamine. *Fed. Proc.* **23**, 836–850 (1964).
5. Wise, R. A. & Bozarth, M. A. A psychomotor stimulant theory of addiction. *Psychol. Rev.* **94**, 469–492 (1987).

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6. Robinson, T. E. & Berridge, K. C. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* **18**, 247–291 (1993).
7. Di Chiara, G. & Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl Acad. Sci. USA* **85**, 5274–5278 (1988).
8. Egerton, A. *et al.* The dopaminergic basis of human behaviors: a review of molecular imaging studies. *Neurosci. Biobehav. Rev.* **33**, 1109–1132 (2009).
9. Volkow, N. D. *et al.* Imaging endogenous dopamine competition with [^{11}C]raclopride in the human brain. *Synapse* **16**, 255–262 (1994).
10. Laruelle, M. *et al.* SPECT imaging of striatal dopamine release after amphetamine challenge. *J. Nucl. Med.* **36**, 1182–1190 (1995).
11. Volkow, N. D. *et al.* Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D2 receptors. *J. Pharmacol. Exp. Ther.* **291**, 409–415 (1999).
12. Boileau, I. *et al.* Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse* **49**, 226–231 (2003).
13. Urban, N. B. *et al.* Sex differences in striatal dopamine release in young adults after oral alcohol challenge: a positron emission tomography imaging study with [^{11}C] raclopride. *Biol. Psychiatry* **68**, 689–696 (2010).
14. Barrett, S. P., Boileau, I., Okker, J., Pihl, R. O. & Dagher, A. The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and ^{11}C raclopride. *Synapse* **54**, 65–71 (2004).
15. Vollenweider, F. X., Vontobel, P., Oye, I., Hell, D. & Leenders, K. L. Effects of S-ketamine on striatal dopamine: a [^{11}C] raclopride PET study of a model psychosis in humans. *J. Psychiatr. Res.* **34**, 35–43 (2000).
16. Bossong, M. G. *et al.* Δ9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology* **34**, 759–766 (2009).
17. Volkow, N. D. *et al.* Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. *JAMA* **301**, 1148–1154 (2009).
18. Jasinski, D. R. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. *J. Psychopharmacol.* **14**, 53–60 (2000).
19. Tye, K. M. *et al.* Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature* **493**, 537–541 (2013).
20. Yoder, K. K. *et al.* Heterogeneous effects of alcohol on dopamine release in the striatum: a PET study. *Alcohol. Clin. Exp. Res.* **31**, 965–973 (2007).
21. Stokes, P. R., Mehta, M. A., Curran, H. V., Breen, G. & Grasby, P. M. Can recreational doses of THC produce significant dopamine release in the human striatum? *Neuroimage* **48**, 186–190 (2009).
22. Barkus, E. *et al.* Does intravenous Δ9-tetrahydrocannabinol increase dopamine release? A SPET study. *J. Psychopharmacol.* **25**, 1462–1468 (2011).
23. Aalto, S. *et al.* Ketamine does not decrease striatal dopamine D2 receptor binding in man. *Psychopharmacol.* **164**, 401–406 (2002).
24. Kegeles, L. S. *et al.* NMDA antagonist effects on striatal dopamine release: positron emission tomography studies in humans. *Synapse* **43**, 19–29 (2002).
25. Welberg, L. Addiction: from mechanisms to treatment. *Nature Rev. Neurosci.* **12**, 621 (2011).
26. Kalivas, P. W. Drug addiction: to the cortex.and beyond! *Am. J. Psychiatry* **158**, 349–350 (2001).
27. Volkow, N. D., Wang, G. J., Fowler, J. S., Tomasi, D. & Telang, F. Addiction: beyond dopamine reward circuitry. *Proc. Natl Acad. Sci. USA* **108**, 15037–15042 (2011).
28. Rothman, R. B. A review of the effects of dopaminergic agents in humans: implications for medication development. *NIDA Res. Monogr.* **145**, 67–87 (1994).
29. Van Ree, J. M. & Ramsey, N. The dopamine hypothesis of opiate reward challenged. *Eur. J. Pharmacol.* **134**, 239–243 (1987).
30. Lingford-Hughes, A. R., Welch, S., Peters, L., Nutt, D. J. & British Association for Psychopharmacology, Expert Reviewers Group. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. *J. Psychopharmacol.* **26**, 899–952 (2012).
31. Daglish, M. R. *et al.* Brain dopamine response in human opioid addiction. *Br. J. Psychiatry* **193**, 65–72 (2008).
32. Watson, B. J. *et al.* Investigating expectation and reward in human opioid addiction with [C] raclopride PET. *Addict. Biol.* **19**, 1032–1040 (2013).
33. Brody, A. L. *et al.* Ventral striatal dopamine release in response to smoking a regular versus a denicotinized cigarette. *Neuropsychopharmacology* **34**, 282–289 (2009).
34. Drevets, W. C. *et al.* Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol. Psychiatry* **49**, 81–96 (2001).
35. Oswald, L. M. *et al.* Relationships among ventral striatal dopamine release, cortisol secretion, and subjective responses to amphetamine. *Neuropsychopharmacology* **30**, 821–832 (2005).
36. Martinez, D. *et al.* Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. *Am. J. Psychiatry* **164**, 622–629 (2007).
37. Wand, G. S. *et al.* Association of amphetamine-induced striatal dopamine release and cortisol responses to psychological stress. *Neuropsychopharmacology* **32**, 2310–2320 (2007).
38. Schneier, F. R. *et al.* Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder. *Depress. Anxiety* **26**, 411–418 (2009).
39. Leyton, M. *et al.* Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[^{11}C]raclopride study in healthy men. *Neuropsychopharmacology* **27**, 1027–1035 (2002).
40. Boileau, I. *et al.* Conditioned dopamine release in humans: a positron emission tomography ^{11}C raclopride study with amphetamine. *J. Neurosci.* **27**, 3998–4003 (2007).
41. Narendran, R. *et al.* A comparative evaluation of the dopamine $D_{2/3}$ agonist radiotracer [^{11}C](−)-*N*-propyl-norapomorphine and antagonist [^{11}C] raclopride to measure amphetamine-induced dopamine release in the human striatum. *J. Pharmacol. Exp. Ther.* **333**, 533–539 (2010).
42. Shotbolt, P. *et al.* Within-subject comparison of [^{11}C]-(+)-PHNO and [^{11}C]raclopride sensitivity to acute amphetamine challenge in healthy humans. *J. Cereb. Blood Flow Metab.* **32**, 127–136 (2012).
43. Montgomery, A. J., Lingford-Hughes, A. R., Egerton, A., Nutt, D. J. & Grasby, P. M. The effect of nicotine on striatal dopamine release in man: a [^{11}C] raclopride PET study. *Synapse* **61**, 637–645 (2007).
44. Fowler, J. *et al.* Inhibition of monoamine oxidase B in the brains of smokers. *Nature* **379**, 733–736 (1996).
45. Mawlawi, O. *et al.* Imaging human mesolimbic dopamine transmission with positron emission tomography: I. accuracy and precision of D2 receptor parameter measurements in ventral striatum. *J. Cereb. Blood Flow Metab.* **21**, 1034–1057 (2001).
46. Volkow, N. D. *et al.* Effects of chronic cocaine abuse on postsynaptic dopamine receptors. *Am. J. Psychiatry* **147**, 719–724 (1990).
47. Volkow, N. D. *et al.* Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* **14**, 169–177 (1993).
48. Volkow, N. D. *et al.* Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J. Neurosci.* **25**, 3932–3939 (2005).
49. Martinez, D. *et al.* Lower level of endogenous dopamine in patients with cocaine dependence: findings from PET imaging of D2/D3 receptors following acute dopamine depletion. *Am. J. Psychiatry* **166**, 1170–1177 (2009).
50. Narendran, R. *et al.* Imaging of dopamine $D_{2/3}$ agonist binding in cocaine dependence: a [^{11}C] NPA positron emission tomography study. *Synapse* **65**, 1344–1349 (2011).
51. Martinez, D. *et al.* Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. *Am. J. Psychiatry* **168**, 634–641 (2011).
52. Volkow, N. D. *et al.* Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am. J. Psychiatry* **158**, 2015–2021 (2001).
53. Lee, B. *et al.* Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J. Neurosci.* **29**, 14734–14740 (2009).
54. Wang, G. J. *et al.* Decreased dopamine activity predicts relapse in methamphetamine abusers. *Mol. Psychiatry* **17**, 918–925 (2012).
55. Volkow, N. D. *et al.* Decreases in dopamine receptors but not in dopamine transporters in alcoholics. *Alcohol. Clin. Exp. Res.* **20**, 1594–1598 (1996).
56. Heinz, A. *et al.* Correlation between dopamine D2 receptors in the ventral striatum and central processing of alcohol cues and craving. *Am. J. Psychiatry* **161**, 1783–1789 (2004).
57. Martinez, D. *et al.* Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. *Biol. Psychiatry* **58**, 779–786 (2005).
58. Hietala, J. *et al.* Striatal D2 dopamine receptor binding characteristics *in vivo* in patients with alcohol dependence. *Psychopharmacology (Berl.)* **116**, 285–290 (1994).
59. Volkow, N. D. *et al.* Effects of alcohol detoxification on dopamine D2 receptors in alcoholics: a preliminary study. *Psychiatry Res.* **116**, 163–172 (2002).
60. Volkow, N. D. *et al.* Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. *J. Neurosci.* **27**, 12700–12706 (2007).
61. Volkow, N. D. *et al.* High levels of dopamine D2 receptors in unaffected members of alcoholic families: possible protective factors. *Arch. Gen. Psychiatry* **63**, 999–1008 (2006).
62. Wang, G. J. *et al.* Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. *Neuropsychopharmacology* **16**, 174–182 (1997).
63. Zijlstra, F., Booij, J., van den Brink, W. & Franken, I. H. Striatal dopamine D2 receptor binding and dopamine release during cue-elicited craving in recently abstinent opiate-dependent males. *Eur. Neuropsychopharmacol.* **18**, 262–270 (2008).
64. Martinez, D. *et al.* Deficits in dopamine D2 receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. *Biol. Psychiatry* **71**, 192–198 (2012).
65. Fehr, C. *et al.* Association of low striatal dopamine D2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *Am. J. Psychiatry* **165**, 507–514 (2008).
66. Brown, A. K. *et al.* Sex differences in striatal dopamine D2/D3 receptor availability in smokers and non-smokers. *Int. J. Neuropsychopharmacol.* **15**, 989–994 (2012).
67. Yang, Y. K. *et al.* Striatal dopamine D2/D3 receptor availability in male smokers. *Psychiatry Res.* **146**, 87–90 (2006).
68. Yang, Y. K. *et al.* Decreased dopamine transporter availability in male smokers — a dual isotope SPECT study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **32**, 274–279 (2008).
69. Scott, D. J. *et al.* Smoking modulation of μ-opioid and dopamine D2 receptor-mediated neurotransmission in humans. *Neuropsychopharmacology* **32**, 450–457 (2007).
70. Sevy, S. *et al.* Cerebral glucose metabolism and D2/D3 receptor availability in young adults with cannabis dependence measured with positron emission tomography. *Psychopharmacology (Berl.)* **197**, 549–556 (2008).
71. Stokes, P. R. *et al.* History of cannabis use is not associated with alterations in striatal dopamine D2/D3 receptor availability. *J. Psychopharmacol.* **26**, 144–149 (2012).
72. Urban, N. B. *et al.* Dopamine release in chronic cannabis users: a [^{11}C]raclopride positron emission tomography study. *Biol. Psychiatry* **71**, 677–683 (2012).
73. Albrecht, D. S. *et al.* Striatal D2/D3 receptor availability is inversely correlated with cannabis consumption in chronic marijuana users. *Drug Alcohol Depend.* **128**, 52–57 (2013).
74. Volkow, N. D. *et al.* Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. *Proc. Natl Acad. Sci. USA* **111**, E3149–E3156 (2014).
75. Volkow, N. D. *et al.* Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *Am. J. Psychiatry* **156**, 1440–1443 (1999).
76. Volkow, N. D. *et al.* Brain DA D2 receptors predict reinforcing effects of stimulants in humans: replication study. *Synapse* **46**, 79–82 (2002).
77. Dalley, J. W. *et al.* Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* **315**, 1267–1270 (2007).

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78. McNamara, R., Dalley, J. W., Robbins, T. W., Everitt, B. J. & Belin, D. Trait-like impulsivity does not predict escalation of heroin self-administration in the rat. *Psychopharmacology* **212**, 453–464 (2010).
79. Nader, M. A. *et al.* PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. *Nature Neurosci.* **9**, 1050–1056 (2006).
80. Thanos, P. K., Michaelides, M., Umegaki, H. & Volkow, N. D. D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. *Synapse* **62**, 481–486 (2008).
81. Thanos, P. K. *et al.* Dopamine D2R DNA transfer in dopamine D2 receptor-deficient mice: effects on ethanol drinking. *Life Sci.* **77**, 130–139 (2005).
82. Volkow, N. D. *et al.* Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature* **386**, 830–833 (1997).
83. Casey, K. F. *et al.* Reduced dopamine response to amphetamine in subjects at ultra-high risk for addiction. *Biol. Psychiatry* **76**, 23–30 (2014).
84. Schultz, W. Predictive reward signal of dopamine neurons. *J. Neurophysiol.* **80**, 1–27 (1998).
85. Nutt, D. J., King, L. A., Phillips, L. D. & Independent Scientific Committee on Drugs. Drug harms in the UK: a multicriteria decision analysis. *Lancet* **376**, 1558–1565 (2010).
86. Badiani, A., Belin, D., Epstein, D., Calu, D. & Shaham, Y. Opiate versus psychostimulant addiction: the differences do matter. *Nature Rev. Neurosci.* **12**, 685–700 (2011).
87. Koepp, M. J. *et al.* Evidence for striatal dopamine release during a video game. *Nature* **393**, 266–268 (1998).
88. Kjaer, T. W. *et al.* Increased dopamine tone during meditation-induced change of consciousness. *Brain Res. Cogn. Brain Res.* **13**, 255–259 (2002).
89. Volkow, N. D. *et al.* Brain dopamine is associated with eating behaviors in humans. *Int. J. Eat. Disord.* **33**, 136–142 (2003).
90. de la Fuente-Fernandez, R. *et al.* Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* **293**, 1164–1166 (2001).
91. Vijayraghavan, S., Wang, M., Birnbaum, S. G., Williams, G. V. & Arnsten, A. F. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nature Neurosci.* **10**, 376–384 (2007).
92. Howes, O. D. *et al.* The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch. Gen. Psychiatry* **69**, 776–786 (2012).
93. Cousins, D. A., Butts, K. & Young, A. H. The role of dopamine in bipolar disorder. *Bipolar Disord.* **11**, 787–806 (2009).
94. Everitt, B. J. & Robbins, T. W. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neurosci. Biobehav. Rev.* **39**, 1946–1954 (2013).
95. Haber, S. N., Fudge, J. L. & McFarland, N. R. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J. Neurosci.* **20**, 2369–2382 (2000).
96. Trifilieff, P. & Martinez, D. Imaging addiction: D2 receptors and dopamine signaling in the striatum as biomarkers for impulsivity. *Neuropharmacology* **76**, 498–509 (2014).
97. Reeves, S. J. *et al.* Limbic striatal dopamine D2/3 receptor availability is associated with non-planning impulsivity in healthy adults after exclusion of potential dissimulators. *Psychiatry Res.* **202**, 60–64 (2012).
98. Clark, L. *et al.* Pathological choice: the neuroscience of gambling and gambling addiction. *J. Neurosci.* **33**, 17617–17623 (2013).
99. Boileau, I. *et al.* The D2/3 dopamine receptor in pathological gambling: a positron emission tomography study with [^{11}C]-(+)-propyl-hexahydro-naphtho-oxazin and [^{11}C] raclopride. *Addiction* **108**, 953–963 (2013).
100. Clark, L. *et al.* Striatal dopamine D2/D3 receptor binding in pathological gambling is correlated with mood-related impulsivity. *Neuroimage* **63**, 40–46 (2012).
101. Boileau, I. *et al. In vivo* evidence for greater amphetamine-induced dopamine release in pathological gambling: a positron emission tomography study with [^{11}C]-(+)-PHNO. *Mol. Psychiatry* **19**, 1305–1313 (2014).
102. O'Sullivan, S. S. *et al.* Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. *Brain* **134**, 969–978 (2011).
103. Volkow, N. D. *et al.* Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J. Neurosci.* **26**, 6583–6588 (2006).
104. Wong, D. F. *et al.* Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology* **31**, 2716–2727 (2006).
105. Volkow, N. D. *et al.* Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues. *Neuroimage* **39**, 1266–1273 (2008).
106. Arnsten, A. F. & Li, B.-M. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biol. Psychiatry* **57**, 1377–1384 (2005).
107. Volkow, N. D. *et al.* Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. *Neuroimage* **42**, 1537–1543 (2008).
108. Ersche, K. D. *et al.* Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. *Arch. Gen. Psychiatry* **67**, 632–644 (2010).
109. Lawford, B. R. *et al.* Bromocriptine in the treatment of alcoholics with the D2 dopamine receptor A1 allele. *Nature Med.* **1**, 337–341 (1995).
110. Levey, A. I. *et al.* Localization of D1 and D2 dopamine receptors in brain with subtype-specific antibodies. *Proc. Natl Acad. Sci. USA* **90**, 8861–8865 (1993).
111. Laruelle, M. *et al.* Microdialysis and SPECT measurements of amphetamine-induced dopamine release in nonhuman primates. *Synapse* **25**, 1–14 (1997).
112. Colasanti, A. *et al.* Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. *Biol. Psychiatry* **72**, 371–377 (2012).
113. Mitchell, J. M. *et al.* Alcohol consumption induces endogenous opioid release in the human orbitofrontal cortex and nucleus accumbens. *Sci. Transl Med.* **4**, 116ra6 (2012).
114. Zubieta, J. K. *et al.* Increased μ opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. *Nature Med.* **2**, 1225–1229 (1996).
115. Gorelick, D. A. *et al.* Imaging brain μ-opioid receptors in abstinent cocaine users: time course and relation to cocaine craving. *Biol. Psychiatry* **57**, 1573–1582 (2005).
116. Williams, T. M. *et al.* Brain opioid receptor binding in early abstinence from opioid dependence: positron emission tomography study. *Br. J. Psychiatry* **191**, 63–69 (2007).
117. Williams, T. M. *et al.* Brain opioid receptor binding in early abstinence from alcohol dependence and relationship to craving: an [^{11}C]diprenorphine PET study. *Eur. Neuropsychopharmacol.* **19**, 740–748 (2009).
118. Weerts, E. M. *et al.* Positron emission tomography imaging of μ- and δ-opioid receptor binding in alcohol-dependent and healthy control subjects. *Alcohol. Clin. Exp. Res.* **35**, 2162–2173 (2011).
119. Heinz, A. *et al.* Correlation of stable elevations in striatal μ-opioid receptor availability in detoxified alcoholic patients with alcohol craving: a positron emission tomography study using carbon 11-labeled carfentanil. *Arch. Gen. Psychiatry* **62**, 57–64 (2005).
120. Mann, K., Bladstrom, A., Torup, L., Gual, A. & van den Brink, W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. *Biol. Psychiatry* **73**, 706–713 (2013).
121. Grant, J. E. *et al.* Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. *Am. J. Psychiatry* **163**, 303–312 (2006).
122. Grant, J. E., Odlaug, B. L., Potenza, M. N., Hollander, E. & Kim, S. W. Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. *Br. J. Psychiatry* **197**, 330–331 (2010).
123. Lingford-Hughes, A. *et al.* A [^{11}C]Ro15 4513 PET study suggests that alcohol dependence in man is associated with reduced α5 benzodiazepine receptors in limbic regions. *J. Psychopharmacol.* **26**, 273–281 (2012).
124. Stokes, P. R. *et al.* History of cigarette smoking is associated with higher limbic $GABA_A$ receptor availability. *Neuroimage* **69**, 70–77 (2013).
125. Laruelle, M. Imaging dopamine transmission in schizophrenia. A review and meta-analysis. *Q. J. Nucl. Med.* **42**, 211–221 (1998).
126. Vilkman, H. *et al.* Measurement of extrastriatal D2-like receptor binding with [^{11}C]FLB 457 — a test-retest analysis. *Eur. J. Nucl. Med.* **27**, 1666–1673 (2000).
127. Ginovart, N. *et al.* Positron emission tomography quantification of [^{11}C]-(+)-PHNO binding in the human brain. *J. Cereb. Blood Flow Metab.* **27**, 857–871 (2007).
128. Erritzoe, D. *et al. In vivo* imaging of cerebral dopamine D3 receptors in alcoholism. *Neuropsychopharmacology* **39**, 1703–1712 (2014).
129. Brody, A. L. *et al.* Smoking-induced ventral striatum dopamine release. *Am. J. Psychiatry* **161**, 1211–1218 (2004).
130. Brody, A. L. *et al.* Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Arch. Gen. Psychiatry* **63**, 808–816 (2006).
131. Takahashi, H. *et al.* Enhanced dopamine release by nicotine in cigarette smokers: a double-blind, randomized, placebo-controlled pilot study. *Int. J. Neuropsychopharmacol.* **11**, 413–417 (2008).

Competing interests statement
The authors declare competing interests: see Web version for details.

FURTHER INFORMATION

***Time* magazine cover on "How we get addicted":** http://content.time.com/time/covers/0,16641,19970505,00.html
Wikipedia entry on "dopamine": http://en.wikipedia.org/wiki/Dopamine
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