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Review

Imaging dopamine's role in drug abuse and addiction

N.D. Volkow*, J.S. Fowler, G.J. Wang, R. Baler, F. Telang

National Institute on Drug Abuse, NIH, Bethesda, MD 20892, USA

A B S T R A C T

Dopamine is involved in drug reinforcement but its role in addiction is less clear. Here we describe PET imaging studies that investigate dopamine's involvement in drug abuse in the human brain. In humans the reinforcing effects of drugs are associated with large and fast increases in extracellular dopamine, which mimic those induced by physiological dopamine cell firing but are more intense and protracted. Since dopamine cells fire in response to salient stimuli, supraphysiological activation by drugs is experienced as highly salient (driving attention, arousal, conditioned learning and motivation) and with repeated drug use may raise the thresholds required for dopamine cell activation and signaling. Indeed, imaging studies show that drug abusers have marked decreases in dopamine D2 receptors and in dopamine release. This decrease in dopamine function is associated with reduced regional activity in orbitofrontal cortex (involved in salience attribution; its disruption results in compulsive behaviors), cingulate gyrus (involved in inhibitory control; its disruption results in impulsivity) and dorsolateral prefrontal cortex (involved in executive function; its disruption results in impaired regulation of intentional actions). In parallel, conditioning triggered by drugs leads to enhanced dopamine signaling when exposed to conditioned cues, which then drives the motivation to procure the drug in part by activation of prefrontal and striatal regions. These findings implicate deficits in dopamine activity—inked with prefrontal and striatal deregulation—in the loss of control and compulsive drug intake that results when the addicted person takes the drugs or is exposed to conditioned cues. The decreased dopamine function in addicted individuals also reduces their sensitivity to natural reinforcers. Therapeutic interventions aimed at restoring brain dopaminergic tone and activity of cortical projection regions could improve prefrontal function, enhance inhibitory control and interfere with impulsivity and compulsive drug administration while helping to motivate the addicted person to engage in non-drug related behaviors.

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1. Introduction

Drugs of abuse trigger large increases in extracellular dopamine (DA) in limbic regions (including nucleus accumbens; NAc) (Di Chiara and Imperato, 1988; Koob and Bloom, 1988), which are associated with their reinforcing effects. These effects mimic but surpass the DA increases secondary to phasic DA cell firing that play a physiological role in coding for saliency and reward (Schultz et al., 2000). Though some animal studies have questioned the extent to which DA increases in NAc are associated with reward (Drevets et al., 2001; Day et al., 2007), human imaging studies have shown that drug-induced increases in DA in the striatum (including the ventral striatum, where the NAc is located) are associated with subjective descriptors of reward (high, euphoria) (Volkow et al., 1996a; Drevets et al., 2001). Nevertheless, it is also evident that the firing rate of DA cells encode not just reward (Tobler et al., 2007)

and expectancy of reward (Volkow et al., 2003b) but also the saliency of a given event or stimulus (Rolls et al., 1984; Williams et al., 1993; Horvitz, 2000; Zink et al., 2003). The saliency of an event is driven either by its unexpectedness, its novelty, its conditioned expectations or its reinforcing effects (positive as well as negative) (Volkow et al., 2003, 2006b). Firing of DA cells, concomitant to the use of the drug will also facilitate the consolidation of memory traces connected to the drug. These, in turn, will trigger DA cells firing with future exposure to stimuli associated with the drug (in expectation of the reward) (Waelti et al., 2001). Because of DA's role in motivation, the DA increases associated with drug-cues or the drug itself are also likely to modulate the motivation to procure the reward (McClure et al., 2003).

The increase in knowledge regarding the multiple roles of DA in the reinforcement processes has led to more complex models of drug addiction. It is currently believed that drugs are reinforcing not just because they are pleasurable but because, by increasing DA, they are being processed as salient stimuli that will inherently motivate the procurement of more drug (regardless of whether the drug is consciously perceived as pleasurable or not).

Brain imaging techniques have contributed greatly to this new understanding. They have allowed us to measure neurochemical and metabolic processes in the living human brain (Volkow et al., 1997a), to investigate the nature of the changes in DA induced by drugs of abuse and their behavioral relevance, and to study the plastic changes in brain DA activity and its functional consequences in drug addicted subjects. This paper provides an updated review of relevant findings.

2. Drug-induced dopamine increases in the human brain and in reinforcement

The use of positron emission tomography (PET) and specific D2 DA receptor radioligands (e.g., [^{11}C]raclopride, [^{18}F]N-methylspiroperidol) has proven invaluable for the study of the relationships between a drug's ability to modulate DA and its reinforcing (i.e., euphorigenic, high-inducing, drug-liking) effects in the human brain. The approach has been used effectively to assess the effects of stimulant drugs (i.e., methylphenidate, amphetamine, cocaine) as well as those of nicotine (Barrett et al., 2004; Brody et al., 2004; Montgomery et al., 2007; Takahashi et al., 2007). Both the intravenous administration of methylphenidate (0.5 mg/kg), which like cocaine, increases DA by blocking DA transporters (DAT) as well as that of amphetamine (0.3 mg/kg), which like methamphetamine, increases DA by releasing it from the terminal via DAT, increase extracellular DA concentration in striatum and such increases are associated with self-reports of "high" and "euphoria" (Hemby et al., 1997; Villemagne et al., 1999). Interestingly, orally administered methylphenidate (0.75–1 mg/kg) also increased DA but is not typically perceived as reinforcing (Chait, 1994; Volkow et al., 2001b). Since intravenous administration leads to fast DA changes whereas oral administration increases DA slowly, the failure to observe the "high" with oral methylphenidate—or amphetamine (Stoops et al., 2007)—is likely to reflect the slower pharmacokinetics (Parasrampuria et al., 2007). Indeed, the speed at which drugs of abuse enter the brain has been recognized as a key parameter affecting its reinforcing effects (Balster and Schuster, 1973; Volkow et al., 1995, 2000). Not surprisingly, the DA increases in ventral striatum induced after smoking, which has similarly very fast rate of brain uptake, are also associated with its reinforcing effects (Brody et al., 2004).

This link between fast brain uptake (leading to fast DA changes) and the reinforcing properties of a given drug suggests the involvement of phasic DA firing. The fast bursts (>30 Hz) generated by phasic release result in abrupt fluctuations in DA levels that contribute to highlight the saliency of a stimulus (Grace, 2000). Such a mechanism stands in contrast to tonic DA cell firing (with slower frequencies of around 5 Hz), which is responsible for maintaining the baseline steady-state DA levels that set the DA system's responsiveness threshold. Therefore, we have proposed that drugs of abuse manage to induce changes in DA concentration that mimic, but greatly exceed, those produced by physiologic phasic DA cell firing. On the other hand the oral administration of stimulant drugs, which is the route used for therapeutic purposes is likely to induce slow DA changes that resemble those associated with tonic DA cell firing (Volkow and Swanson, 2003). Because stimulant drugs block DATs, which are the main mechanism for DA removal (Williams and Galli, 2006), they could—even when given orally—increase the reinforcing value of other reinforcers (natural or drug rewards) (Volkow et al., 2001b). Similarly, nicotine, which facilitates DA cell firing, also enhances the reinforcing value of stimuli with which it is paired. In the latter case the combination of nicotine with the natural reward becomes inextricably linked to its reinforcing effects.

3. Role of dopamine in the long-term effects of drugs of abuse on DA in the human brain: involvement in addiction

Synaptic increases in DA occur during drug intoxication in both addicted as well as non-addicted subjects (Di Chiara and Imperato, 1988; Koob and Bloom, 1988). However, only a minority of exposed subjects—the actual proportion being a function of the type of drug used—ever develops a compulsive drive to continue taking the drug (Schuh et al., 1996). This indicates that the acute drug-induced DA increase alone cannot explain the ensuing development of addiction. Because drug addiction requires chronic drug administration, it is likely to be rooted—in vulnerable individuals—in the repeated perturbation of the DA system, triggering neuro-adaptations in reward/saliency, motivation/drive, inhibitory control/executive function and memory/conditioning circuits, all of which are modulated by dopaminergic pathways (Volkow et al., 2003a).

Consistent with this line of thought, there is mounting evidence that exposure to stimulants, nicotine, or opiates produces persistent adaptive changes in the structure of dendrites and dendritic spines on cells in key areas of the brain with roles in motivation, reward, judgment, and the inhibitory control of behavior (Robinson and Kolb, 2004). For example, chronic adaptations in DA receptor signaling may trigger compensatory glutamate receptor responses with the potential to affect synaptic plasticity (Wolf et al., 2003). The fact that DA (Wolf et al., 2003; Liu et al., 2005), but also glutamate, GABA, and other neurotransmitters, are all highly versatile modulators of synaptic plasticity, draws a direct path connecting the effects of drugs of abuse with the adaptive alterations, not only in the reward center but also in many other circuits, through the strengthening, formation, and elimination of synapses.

Multiple radiotracers have been used to detect and measure these types of changes in targets within DA network in the human brain (Table 1). Using [^{18}F]N-methylspiroperidol or [^{11}C]raclopride we and others (Martinez et al., 2004, 2005, 2007) have shown that subjects addicted to a wide variety of drugs (cocaine, heroin,

Table 1
Summary of PET findings comparing various targets involved in DA neurotransmission between substance abusers and control subjects for which statistically significant differences between the groups were identified

Target investigated	Drug used	Finding	Reference
D2 DA receptors	Cocaine	↓ Acute withdrawal	Volkow et al., 1993
		↓ Detoxified	Volkow et al., 1993, 1996b
	Alcohol	↓ 1–68 week abstinence	Hietala et al., 1994
		↓ Detoxified	Volkow et al., 2002d
	Methamphetamine	↓ Detoxified	Volkow et al., 2001a
	Heroin	↓ Active user	Wang et al., 1997
	Nicotine	↓ Active user	Fehr et al., 2008
	Cannabis	0 Detoxified	Sevy et al., 2008
DA transporters	Cocaine	↑ 4 weeks abstinence	Malison et al., 1998
		0 Detoxified	Volkow et al., 1996b
	Alcohol	↓ Acute withdrawal	Laine et al., 1999
		0 Detoxified	Volkow et al., 1996c
	Methamphetamine	↓ Detoxified	Chang et al., 2007
	Cigarettes	↓ Active user	Yang et al., 2008
Vesicular monoamine transporters-2	Methamphetamine	↓ Detoxified	Chang et al., 2007
Metabolism (MAOB)	Cigarettes	↓ Active user	Fowler et al., 2003
Synthesis (dopa decarboxylase)	Cocaine	↓ Detoxified	Wu et al., 1997
	Alcohol	0 Detoxified	Heinz et al., 2005
DA release	Cocaine	↑ Active user	Schlaepfer et al., 1997
		↓ Detoxified	Volkow et al., 1997b
	Alcohol	↓ Detoxified	Volkow et al., 2007d

Modified and updated with permission based on Volkow et al. (2007a).

alcohol, and methamphetamine), exhibit significant reductions in D2 DA receptor availability in the striatum (including ventral striatum) that persist months after protracted detoxification (Volkow et al., 2007a). Similar findings were also recently reported in nicotine dependent subjects (Fehr et al., 2008).

It is also relevant to point out in this context that the striatal increases in DA induced by intravenous methylphenidate or intravenous amphetamine (assessed with [^{11}C]raclopride) in cocaine abusers and alcoholics are at least 50% lower than in control subjects (Volkow et al., 1997b; Martinez et al., 2007). Since DA increases induced by methylphenidate are dependent on DA release—a function of DA cell firing—it is reasonable to hypothesize that the difference likely reflects decreased DA cell activity in these drug abusers.

It is important to keep in mind that the results of PET studies done with [^{11}C]raclopride, which is sensitive to competition with endogenous DA, are merely a reflection of vacant D2 DA receptors available to bind to the tracer. Thus, any reduction in D2 DA receptor availability as measured with [^{11}C]raclopride could reflect either decreases in levels of D2 DA receptors and/or increases in DA release (competing for binding with [^{11}C]raclopride for the D2 receptors) in striatum (including NAc). However the fact that cocaine abusers when given i.v. MP showed blunted reductions in specific binding (indicative of decreased DA release) indicates that in cocaine abusers there is both a reduction in the levels of D2 receptors as well as a decrease in DA release in striatum. Each would contribute to the decreased sensitivity in addicted subjects to natural reinforcers (Volkow et al., 2002b). Because drugs are much more potent at stimulating DA-regulated reward circuits than natural reinforcers, drugs would still be able to activate the depressed reward circuits. This decreased sensitivity, on the other hand would result in a reduced interest for environmental stimuli, possibly predisposing subjects for seeking drug stimulation as a means to temporarily activate these reward circuits. As time progresses, the chronic nature of this behavior may explain the transition from taking drugs in order to feel "high" to taking them just to feel normal.

What are the metabolic and functional correlates of such long term drug-induced perturbation in dopaminergic balance? Using the PET radiotracer [^{18}F]fluoro-deoxyglucose (FDG) that measures regional brain glucose metabolism, we and others have shown decreased activity in orbitofrontal cortex (OFC), cingulate gyrus (CG) and dorsolateral prefrontal cortex (DLPFC) in addicted subjects (alcoholics, cocaine abusers, marihuana abusers) (London et al., 1990; Galynker et al., 2000; Ersche et al., 2006; Volkow et al., 2007a). Moreover, in cocaine (Volkow and Fowler, 2000) and methamphetamine (Volkow et al., 2001a) addicted subjects and in alcoholics (Volkow et al., 2007d), we have shown that the reduced activity in OFC, CG and DLPFC is associated with decreased availability of D2 DA receptors in striatum (see Fig. 1 for cocaine and methamphetamine results). Since the OFC, CG and DLPFC are involved with inhibitory control (Goldstein and Volkow, 2002) and with emotional processing (Phan et al., 2002), we had postulated that their abnormal regulation by DA in addicted subjects could underlie their loss of control over drug intake and their poor emotional self-regulation. Indeed, in alcoholics, reductions in D2 DA receptor availability in ventral striatum have been shown to be associated with alcohol craving severity and with greater cue-induced activation of the medial prefrontal cortex and anterior CG, as assessed with fMRI (Heinz et al., 2004). In addition, because damage to the OFC results in perseverative behaviors (Rolls, 2000)—and in humans impairments in OFC and CG are associated with obsessive compulsive behaviors (Saxena et al., 2002)—we have also postulated that DA impairment of these regions could underlie the compulsive drug intake that characterizes addiction (Volkow et al., 2005).

However, the association could also be interpreted to indicate that impaired activity in prefrontal regions could put individuals at risk for drug abuse and that only then the repeated drug use could result in the downregulation of D2 DA receptors.

DA also modulates the activity of the hippocampus, amygdala and dorsal striatum, which are regions implicated in memory, conditioning, and habit formation (Volkow et al., 2002a). Moreover, adaptations in these regions have been documented in preclinical models of drug abuse (Kauer and Malenka, 2007). Indeed, there is increasing recognition of the relevance and likely involvement of memory and learning mechanisms in drug addiction (Vanderschuren and Everitt, 2005). The effects of drugs of abuse on
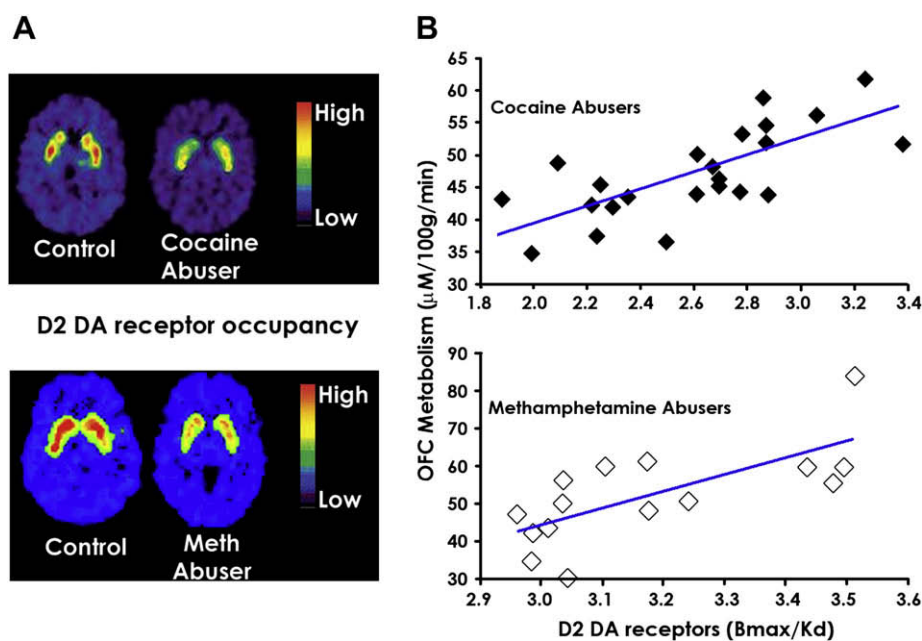

Fig. 1. (A) Normalized volume distribution of [^{11}C]raclopride binding in the striatum of cocaine and methamphetamine abusers and non-drug-abusing comparison subjects. (B) Correlation of DA receptor availability (B_{max}/K_d) in the striatum with measures of metabolic activity in the orbitofrontal cortex (OFC) in cocaine (closed diamonds) and methamphetamine (open diamonds) abusers. Modified with permission based on Volkow et al. (1993, 2001a).

memory systems suggest ways that neutral stimuli can acquire reinforcing properties and motivational salience—that is, through conditioned-incentive learning. In research on relapse, it has been very important to understand why drug addicted subjects experience an intense desire for the drug when exposed to places where they have taken the drug, to people with whom prior drug use had occurred, and to paraphernalia used to administer the drug. This is clinically relevant since exposure to conditioned cues (stimuli that had become strongly linked to the drug experience) is a key contributor to relapse. Since DA is involved with prediction of reward (Schultz, 2002), DA has been predicted to underlie the conditioned responses that trigger craving. Preclinical studies support this hypothesis: when neutral stimuli are paired with a drug, animals will—with repeated associations—acquire the ability to increase DA in NAc and dorsal striatum when exposed to the now conditioned cue. Predictably, these neurochemical responses have been found to be associated with drug-seeking behavior (Vanderschuren and Everitt, 2005).

In humans, PET studies with [^{11}C]raclopride recently confirmed this hypothesis by showing that in cocaine abusers drug cues (cocaine-cue video of scenes of subjects taking cocaine) significantly increased DA in dorsal striatum, and that these increases were also associated with cocaine craving (Volkow et al., 2006c; Wong et al., 2006) in a cue-dependent fashion (Volkow et al., 2008). Because the dorsal striatum is implicated in habit learning, this association is likely to reflect the strengthening of habits as chronicity of addiction develops. This suggests that the DA-triggered conditioned responses that form, first habits and then compulsive drug consumption, may reflect a fundamental neurobiological perturbation in addiction. It is likely that these conditioned responses involve adaptations in cortico-striatal glutamatergic pathways that regulate DA release (Vanderschuren and Everitt, 2005).

To assess if cue-induced DA increases reflect a primary or a secondary response to the cue a recent imaging study in cocaine addicted subjects evaluated the effects of increasing DA (achieved by oral administration of methylphenidate), with and without the cue, in an attempt to determine whether DA increases by themselves could induce craving. The results of the study revealed a clear dissociation between oral methylphenidate-induced DA increases and cue-associated cravings (Volkow et al., 2008) suggesting that cue-induced DA increases are not the primary effectors but rather reflect downstream stimulation of DA cells (cortico-striatal glutamatergic pathways that regulate DA release; Kalivas and Volkow, 2005). This observation further illuminates the subtle effects of DA firing rate upon addiction circuitry, for the failure of methylphenidate-induced DA increases to induce craving in this paradigm could be explained by the slow nature of the DA increases. On the other hand, fast DA changes as triggered by phasic DA cell firing—as a secondary response to the activation of descending pathways—may underlie the successful induction of cravings with exposure to a cue. It is worth highlighting, that Martinez et al. reported a negative correlation between the DA increases induced by intravenous amphetamine in cocaine abusers and their choice of cocaine over money when tested on a separate paradigm (Martinez et al., 2007). That is, the subjects that showed the lower DA increases when given amphetamine were the ones more likely to select cocaine over a monetary reinforcer. Because in their studies they also reported reduced DA increases in cocaine abusers when compared with controls this could indicate that cocaine abusers with the most severe decreases in brain dopaminergic activity are the ones more likely to choose cocaine over other reinforcers.

4. DA and vulnerability to drug abuse

Understanding why some individuals are more vulnerable to becoming addicted to drugs than others remains one of the most challenging questions in drug abuse research. In healthy non-drug abusing controls we showed that D2 DA receptor availability in the striatum modulated their subjective responses to the stimulant drug methylphenidate. Subjects describing the experience as pleasant had significantly lower levels of receptors compared with those describing methylphenidate as unpleasant (Volkow et al., 1999, 2002c). This suggests that the relationship between DA levels and reinforcing responses follows an inverted u-shaped curve: too little is suboptimal for reinforcement while too much may become aversive. Thus, high D2 DA receptor levels could protect against drug self administration. Support for this is provided by preclinical studies, which showed that higher levels of D2 DA receptors in NAc significantly reduced alcohol intake in animals previously trained to self-administer alcohol (Thanos et al., 2001) and the tendency of group-housed cynomolgus macaques to self-administer cocaine (Morgan et al., 2002), and by clinical studies showing that subjects who despite having a dense family history of alcoholism were not alcoholics had significantly higher D2 DA receptors in striatum than individuals without such family histories (Volkow et al., 2006a). The higher the D2 DA receptors in these subjects, the higher their metabolism in OFC and CG. Thus we can postulate that high levels of D2 DA receptors may protect against alcoholism by modulating frontal circuits involved in salience attribution and inhibitory control.

On the other end of the spectrum, we have found evidence of depressed dopamine activity in specific brain regions of adults with ADHD compared to controls. Deficiencies were seen at the level of both D2 DA receptors and DA release in the caudate (Volkow et al., 2007b) and in the ventral striatum (Volkow et al., 2007c). And, consistent with the current model, the depressed DA phenotype was associated with higher scores on self-reports of methylphenidate liking (Volkow et al., 2007b). Interestingly, if left untreated, individuals with ADHD have a high risk for substance abuse disorders (Elkins et al., 2007).

Finally, sex differences in addictive disorders have been observed repeatedly, and it would be reasonable to ask whether imaging studies could substantiate the preclinical evidence suggesting such differences are due in part to striatal DA system differences and/or whether they result from differences in activity of prefrontal regions (Koch et al., 2007). Indeed, recent studies have documented sexually dimorphic patterns of amphetamine-induced striatal DA release (Munro et al., 2006; Riccardi et al., 2006) that could impact substance abuse vulnerability differently in men and women; although the data do not permit at this point a clear cut conclusion as to whether men or women display greater DA responses. It is also likely that the patterns will be sensitive to experimental conditions, such as context, age and stage of menstrual cycle.

When combined, these observations provide critical insight into the striatal DA's system contribution to addiction vulnerability, to the emergence of frequent psychiatric comorbid pairings, and to the observed sexually dimorphic patterns of substance abuse.

5. Treatment implications

Imaging studies have corroborated the role of DA in the reinforcing effects of drugs of abuse in humans and have extended traditional views of DA involvement in drug addiction. These findings suggest multiprong strategies for the treatment of drug addiction that should attempt to (a) decrease the reward value of the drug of choice and increase the reward value of non-drug reinforcers; (b) weaken conditioned drug behaviors, and the motivational drive to take the drug; and (c) strengthen frontal inhibitory and executive control. Not discussed in this review is the critical involvement of circuits that regulate emotions and response to stress (Koob and Le Moal, 1997) as well as those

responsible for interoceptive perception of needs and desires (Gray and Critchley, 2007), which are also potential targets for therapeutic interventions.

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