

Role of Dopamine, the Frontal Cortex and Memory Circuits in Drug Addiction: Insight from Imaging Studies

Nora D. Volkow,* Joanna S. Fowler,† Gene-Jack Wang,* and Rita Z Goldstein*

**Medical Department and Chemistry Department, Brookhaven National Laboratory,
Upton, New York 11973*

Drug addiction is characterized by a set of recurring processes (intoxication, withdrawal, craving) that lead to the relapsing nature of the disorder. We have used positron emission tomography to investigate in humans the role of dopamine (DA) and the brain circuits it regulates in these processes. We have shown that increases in DA are associated with the subjective reports of drug reinforcement corroborating the relevance of drug-induced DA increases in the rewarding effects of drugs in humans. During withdrawal we have shown in drug abusers significant reductions in DA D2 receptors and in DA release. We postulate that this hypodopaminergic state would result in a decreased sensitivity to natural reinforcers perpetuating the use of the drug as a means to compensate for this deficit and contributing to the anhedonia and dysphoria seen during withdrawal. Because the D2 reductions are associated with decreased activity in the anterior cingulate gyrus and in the orbito-frontal cortex we postulate that this is one of the mechanisms by which DA disruption leads to compulsive drug administration and the lack of control over drug intake in the drug-addicted individual. This is supported by studies showing that during craving these frontal regions become hyperactive in proportion to the intensity of the craving. Craving is also associated with activation of memory circuits including the amygdala (implicated in conditioned learning), hippocampus (implicated in declarative learning), and dorsal striatum (implicated in habit learning) all of which receive DA innervation. We therefore postulate that dopamine contributes to addiction by disrupting the frontal cortical circuits that regulate motivation, drive, and self-control and by memory circuits that increase the motivational salience of the drug and drug-associated stimuli. © 2002 Elsevier Science (USA)

This research was supported in part by the U.S. Department of Energy (Office of Biological and Environmental Research), the National Institute of Drug Abuse (Grants DA 06891, DA 09490, and DA 06278), the National Institute on Alcohol Abuse and Alcoholism (AA 09481), and the Office of National Drug Control Policy.

Address correspondence and reprint requests to Nora D. Volkow, Medical Department, Brookhaven National Laboratory, Upton, New York 11973. Fax: (631) 344-5260. E-mail: volkow@bnl.gov.

Drug addiction is a disorder that results from the complex interplay of chronic drug administration and genetic and environmental variables. The biological mechanisms underlying drug addiction are not well understood. Nor is there knowledge of the mechanisms by which genetic or environmental variables favor or protect against addiction. We have used imaging to investigate the molecular and functional changes in the human brain that lead to the loss of control and the compulsive drug self-administration observed in the addicted subject and to investigate variables associated with vulnerability to drug abuse. For this purpose we have used positron emission tomography (PET), an imaging technology that allows us to measure the concentration of compounds that are of physiological relevance such as receptors, transporters, and enzymes in the human brain. We have investigated cocaine, heroin, marijuana, and methamphetamine (METH) abusers and alcoholics to assess if there are common abnormalities in the brain of these subjects that may point to disruptions responsible for the loss of control in addicted subjects.

Drug addiction is characterized by a set of recurring processes (intoxication, withdrawal, craving) that contribute to the relapsing nature of the disorder. The reinforcing effects of drugs during intoxication set the initial stage that if perpetuated can result in addiction. The ability of drugs of abuse to increase the concentration of dopamine (DA) in the nucleus accumbens (NAc) is considered to be crucial to their reinforcing effects (Koob & Bloom, 1988). However, the DA increases during intoxication cannot explain the process of addiction since drugs of abuse increase DA both in addicted and in nonaddicted subjects. Moreover, the magnitude of the drug-induced DA increases appears to be smaller in addicted than in nonaddicted subjects (Volkow, Wang, Fowler et al., 1997). Nor is there evidence that the pleasurable response to the drug is the pertinent variable since it is not necessarily more intense in addicted than in nonaddicted subjects (Volkow, Wang, Fowler, et al., 1997). Since drug addiction requires chronic drug administration it is possible that addiction results from the repeated perturbation of the DA system (marked DA increases followed by DA decreases) and the consequent disruption of the circuits that it regulates. Most of the preclinical studies have demonstrated a role of the mesolimbic and mesocortical DA circuits in drug self-administration. However, more recent studies are starting to provide evidence of the relevance of the nigrostriatal circuit in addiction (White, 1996). The mesolimbic pathway, which includes the NAc, amygdala, and hippocampus, is relevant for drug reward and for drug-related memories and conditioned responses (Koob & Bloom, 1988). The mesocortical pathway, which includes the cingulate gyrus (CG) and orbitofrontal cortex (OFC) may be relevant for the compulsive drug administration and poor inhibitory control within the context of impaired incentive motivation and emotional valence seen in addiction (Volkow & Fowler, 2000). The nigrostriatal pathway, which includes the dorsal striatum, may be relevant for habit formation associated with chronic drug use (White, 1996).

The strategy we have used to investigate the role of DA in drug reinforcement and addiction is to simultaneously measure brain DA function using PET and assess by self-report the descriptors that relate to drug effects such as "high," "craving," and "drug liking." These self-reports of drug effects serve as tools that provide us with a measure of the subjective experience of the drug-addicted subject. They have been shown to be reliable and consistent across studies and there is no other measure that is better in predicting administration of drugs in humans (Fischman & Foltin, 1991). However, we do not imply equating these descriptors with addiction itself and although this strategy

is a powerful one to show associations with brain function, its correlational nature precludes direct mechanistic interpretation of the results. For this reason, we systematically evaluated the brain–behavior associations using at least two different drugs and where permissible we tested our human-subject derived hypotheses in a preclinical model.

DA INVOLVEMENT IN DRUG INTOXICATION

We used PET to investigate the extent to which the drug-induced increases in DA that had been shown in preclinical studies are also associated with the reinforcing effects of drugs of abuse in humans. We studied this relationship for the psychostimulant drugs cocaine and methylphenidate (MP), both of which increase extracellular DA by blocking DA transporters (DAT) (Ritz, Lamb, Goldberg, & Kuhar, 1987).

We first measured the levels of DAT occupancy by different doses of intravenous (iv) cocaine in active cocaine abusers (Volkow, Wang, Fischman, et al., 1997) and of iv MP in normal controls (Volkow, Wang, Fowler, Logan, Gatley, et al., 1999). Cocaine was very effective in blocking DAT; at the doses commonly abused by cocaine abusers (0.3 and 0.6 mg/kg) it blocked more than 60% of the DAT. MP was also very effective in blocking DAT and a 0.1 mg/kg dose blocked 60% of the DAT. The ED₅₀ (dose required to block 50% of the DAT) for MP was half that required for cocaine (MP, 0.075 mg/kg; cocaine, 0.13 mg/kg). The differences in the ED₅₀ between cocaine and MP are compatible with differences in their affinities for DAT (K_i for inhibition of DA uptake corresponds to 640 and 390 nM, respectively) (Ritz et al., 1987). For both drugs the higher the levels of DAT blockade the higher the intensity of the high (Fig. 1A) and for these drugs to induce a high they had to block more than 50% of the DAT. However, there were subjects who despite having DAT occupancies greater than 50% did not perceive the high (Fig. 1A), which suggests that other variable(s) are required for the high. Although both cocaine and MP are DAT blockers (Ritz et al., 1987) their ability to increase extracellular DA is not only a function of DAT blockade but also of the rate of DA release. Thus we postulated that the reason there were subjects who did not experience the high even with significant DAT blockade was that in those subjects the drug was unable to significantly increase DA (i.e., subjects had low DA release).

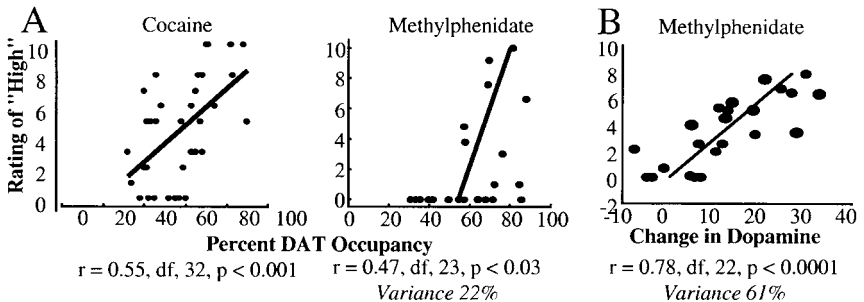


FIG. 1. (A) Correlation between the levels of DA transporter (DAT) blockade and the self-report of high after intravenous cocaine in cocaine abusers and after intravenous MP in normal controls. (B) Correlation between the changes in extracellular DA as assessed by changes in [¹¹C]raclopride and the self-report of high after intravenous MP in normal controls. The changes in DA induced by MP accounted for a larger percent of the variance (61%) in the self-reports of high after iv MP than the levels of DAT blockade (22%).

To test this hypothesis we used PET and [^{11}C]raclopride (radioligand whose binding to D2 receptors is sensitive to competition with endogenous DA (Volkow et al., 1994)) to measure changes in brain DA after different doses of iv MP in healthy controls. The intensity of the high induced by MP was significantly correlated with the levels of released DA; subjects having the greatest increases were those that perceived the most intense high (Fig. 1B). Furthermore, subjects for whom MP did not increase DA did not perceive a high. MP-induced increases in DA, as assessed by its occupation of DA D2 receptors, was a much better predictor of the intensity of the high (accounted for 61% of the variance) than were the levels of DAT blockade (accounted for 22% of the variance). These findings corroborated that stimulant induced high, a mood descriptor that reflects reinforcing effects of drugs in humans (Fischman & Foltin, 1991), is associated with increases in brain DA.

DOPAMINE INVOLVEMENT IN DRUG ADDICTION

PET imaging studies have investigated the various elements involved in DA neurotransmission. To assess the activity of DA neurons we measured the changes in extracellular DA induced by MP; since MP is a DAT blocker the DA increases reflect levels of DAT blockade and magnitude of DA release. When compared with controls, cocaine abusers showed a marked decrease in DA cell activity as evidenced by the reduced changes in striatal [^{11}C]raclopride binding with MP (cocaine abusers were 50% lower than controls) (Volkow, Wang, Fowler, et al., 1997a). The self-reports of high induced by iv MP were also more intense in controls than in the cocaine abusers, whereas in cocaine abusers but not in controls, MP induced intense cocaine craving. In contrast, cocaine abusers showed an increased response to MP in the thalamus, which was not seen in controls and which was associated with cocaine craving. These results challenge the notion that addiction involves an enhanced striatal DA response to the drug (sensitization) or an enhanced induction of euphoria. The abnormal activation of the thalamus in dependent subjects, but not in controls, and its significant association with MP-induced cocaine craving suggests that abnormal activation of thalamic DA pathways may participate in the expression of this unique behavior of the addicted subject. The thalamus has a relatively high uptake of cocaine (Madras & Kaufman, 1994), it is sensitive to DA D2 receptor mediated effects of cocaine (Shyu, Kiritsy-Roy, Morrow, & Casey, 1992), and one of its nuclei, the mediodorsal, which receives DA projections (Groenewegen, 1988) appears to be involved in conditioned reinforcement (Mc Alonan, Robbins, & Everitt, 1993). However, because the specific to nonspecific binding ratio of [^{11}C]raclopride in the thalamus is quite low we cannot exclude the possibility that MP-induced changes in the thalamus in cocaine-dependent subjects reflects nonspecific effects and further studies are required to replicate these findings.

To assess changes in postsynaptic DA targets we evaluated DA D2 receptors in the same subject, which mostly reflect postsynaptic receptors in GABA cells, and regional brain glucose metabolism, which we use as an indicator of regional brain function. PET studies measuring DA D2 receptors have consistently shown long-lasting decreases in DA D2 receptors in drug abusers when compared with controls (reviewed Volkow & Fowler, 2000) (Table 1) (Fig. 2). We have postulated that the decreases in DA D2 receptors coupled with the decreases in DA brain function in the drug abusers would result in a decreased sensitivity of reward circuits to stimulation by natural reinforcers. This decreased

TABLE I.
Summary for the Results of Imaging Studies Measuring DA D2 Receptor Availability (Bmax/Kd) in the Dorsal Striatum (caudate and putamen) with [¹¹C]raclopride in Controls and in Drug Abusers

	Controls Bmax/Kd	Abusers Bmax/Kd	<i>p</i>
Alcoholics	2.71 ± 0.6 (<i>n</i> = 17)	2.10 ± 0.5 (<i>n</i> = 10)	0.05
Heroin abusers	2.97 ± 0.5 (<i>n</i> = 11)	2.44 ± 0.4 (<i>n</i> = 11)	0.01
Cocaine abusers	2.90 ± 0.3 (<i>n</i> = 23)	2.59 ± 0.3 (<i>n</i> = 20)	0.01
METH abusers	2.81 ± 0.3 (<i>n</i> = 20)	2.45 ± 0.3 (<i>n</i> = 15)	0.001

sensitivity would lead to decreased motivational salience for day to day environmental stimuli, possibly predisposing subjects to seek drug stimulation as a means to temporarily activate these reward circuits. Indeed, imaging studies have started to provide evidence of disrupted sensitivity to natural reinforcers in the reward circuits of drug-addicted subjects. One study of opiate addicts showed that different from controls, these subjects did not activate the meso-striatal and meso-corticolimbic circuits in response to natural reinforcers (Martin-Soelch et al., 2001). We have also shown decreased sensitivity to alcohol in brain reward circuits in active cocaine abusers when compared to controls (Volkow & Fowler, 2000). These findings suggest an overall reduction in the sensitivity of the reward circuits in the drug-addicted individual to natural reinforcers and possibly to drugs that are not the drug of addiction, thereby providing a putative mechanism underlying the dysphoria and the anhedonia experienced during withdrawal.

In detoxified cocaine abusers in whom we also measured regional brain glucose metabolism, we showed that the reductions in DA D2 receptors were associated with decreased

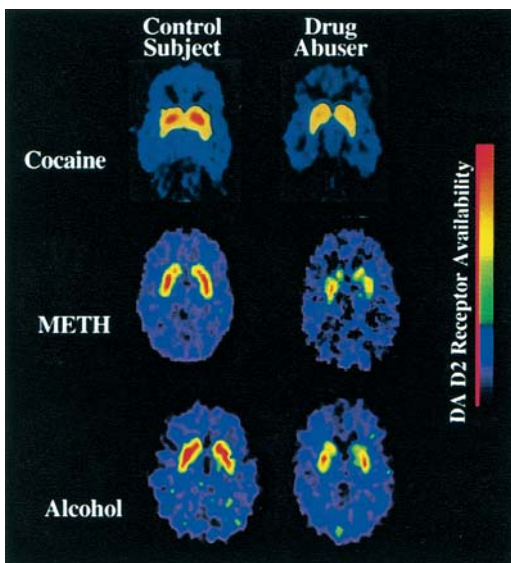


FIG. 2. Brain images of DA D2 receptors at the level of the striatum in control subjects and drug abusers. Images were obtained with [¹¹C]raclopride.

activity in anterior CG and OFC (Volkow et al., 1993) (Fig. 3). We recently replicated these findings in detoxified METH abusers in whom the availability of DA D2 receptors was associated with OFC activity (Volkow et al., 2001). These associations could either reflect a disruption of these cortical brain regions secondary to the changes in DA activity or alternatively it could be interpreted as indicating a primary disruption of the frontal regions, which then deregulate DA cell activity.

In contrast to the decrements in metabolic activity observed in detoxified cocaine abusers we had shown that in active cocaine abusers the OFC was hypermetabolic in proportion to the intensity of the craving that the subjects reported during the study (Volkow et al., 1991). Thus we postulated that during cocaine intoxication the increase in DA facilitates activation of the OFC and the anterior CG, which leads to the craving and subsequent impulsive and compulsive drug intake characteristic of the addicted individual. During withdrawal the OFC (which signals relative saliency of stimuli (Elliott, Dolan, & Frith 2000)) and the anterior CG (which is involved in attention (Posner, 1994) and in selection of motor responses associated to reward (Shima & Tanji, 1998)) are hypometabolic (Volkow et al., 1993), which we postulate is due to lack of stimulation by salient stimuli during detoxification. We therefore postulated that exposure to drug-related stimuli in the withdrawal state can reactivate the OFC and CG and reinitiate the craving for the drug. To test this hypothesis we assessed the effects of iv MP on regional brain glucose metabolism in cocaine abusers tested at least 1 week after cocaine discontinuation, using PET and FDG (Volkow, Wang, Fowler, Hitzemann, et al., 1999). Cocaine abusers, in contrast to normal subjects, showed significant MP-induced increases in metabolism in the anterior CG. Activation of the anterior CG in cocaine abusers has also been reported after administration of cocaine (Breiter et al., 1997) and during cue-induced cocaine craving (Maas et al., 1998). Thus CG activation in the cocaine abusers could reflect the fact that cocaine abusers report the effects of MP to be similar to those of cocaine—when asked to describe the effects of iv MP, cocaine abusers reported it felt similar to cocaine except that it made them more restless and made their heart beat faster (Wang, et al., 1997). In the cocaine abusers, MP also increased metabolism in the OFC in the subjects in whom MP induced intense craving. The OFC processes information about the expectation (Schultz, Tremblay, & Hollerman, 2000) and the value of reward (Elliott, Dolan, et al., 2000). Hence the differential activation of the OFC in subjects that reported intense craving could reflect their expectations of further reward and the value of MP as a reinforcer.

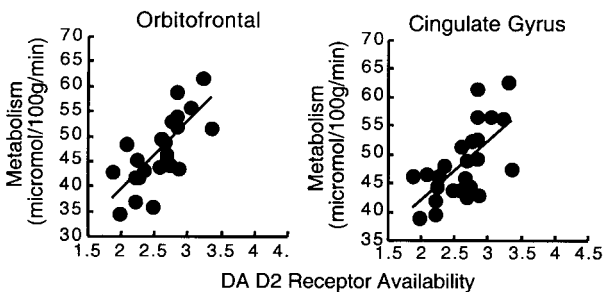


FIG. 3. Correlation between DA D2 receptor availability (ratio index obtained with [18]N-methylspiroperidol) and glucose metabolism in orbitofrontal cortex (OFC) and anterior cingulate gyrus (CG) ($\mu\text{mol}/100/\text{g}/\text{min}$) in detoxified cocaine abusers. Modified from Volkow et al., 2000.

To summarize, there are several ways by which the OFC and the CG could underlie addictive behaviors. (1) The OFC and the CG are involved in the regulation of motivation and drive (Tucker, Luu, & Pribham, 1995), and thus enhanced activation secondary to drug-induced DA stimulation could result in an intense drive to self-administer the drug in the addicted subjects. Its decreased activation during withdrawal could also account for the enhanced salience to the drug to which they are addicted and related stimuli and the decreased salience to non-drug-related stimuli. (2) The OFC has been implicated in the occurrence of compulsive behaviors (reviewed Insel, 1992) and thus one could postulate that its inappropriate activation could induce compulsive drug administration in the drug-addicted subject. In laboratory animals damage of the OFC results in perseveration and resistance to extinction of reward-associated behaviors (Rolls, 2000). This is reminiscent of the reports by drug addicts who claim that once they start taking the drug they cannot stop even when the drug is no longer pleasurable. In extrapolating from findings from OFC lesions it is worth noting that recent imaging studies have provided evidence of structural changes in the OFC of cocaine-addicted subjects (Franklin et al., 2002). (3) The OFC is involved with learning stimulus-reinforcement associations and with conditioned responses (Rolls, 2000) and could therefore participate in cues or drug-induced craving. Laboratory animals exposed to an environment where they had received a drug of abuse show activation of the OFC (Brown, Robertson, & Fibiger, 1992) and lesions of the OFC interfere with drug-induced conditioned place preference (Isaac, Nonneman, Neisewander, Landers, & Bardo, 1989). This is relevant because drug-induced conditioned responses have been implicated in the craving elicited in humans by drug-related stimuli, which is one of the factors that contribute to relapse in drug abusers. Indeed, activation of the OFC has been shown in drug abusers during craving elicited by taking a drug (Volkow, Wang, Fowler, Hitzemann, et al., 1999), by viewing a video of drug paraphernalia (Grant et al., 1996), and by recalling previous drug experiences (Wang et al., 1999). (4) The OFC processes information associated with the prediction (Schultz et al., 2000) and the value of reward (Elliott, Rubinsztein, et al., 2000) and hence its hyperactivation during cue-exposure could signal reward prediction, which contributes to the experience of craving. (5) The CG is involved with mood regulation (Devinsky, Morrell, & Vogt, 1995) and its disruption could underlie the dysphoria reported during drug withdrawal, which is a contributor to relapse. (6) The OFC and the CG are associated with decision making (Bechara et al., 2000, Gehring & Willoughby, 2002). Their disruption could lead to inadequate decisions that favor immediate rewards over delayed but more favorable responses. (7) The CG also participates in inhibitory control of emotional responses (Bokura, Yamaguchi, & Kobayashi, 2001); hence its disruption could contribute to an inability to control the intake of the drug under emotionally stressful situations.

ROLE OF DA IN PREDISPOSITION TO DRUG ABUSE

The studies documenting reductions in DA D2 receptors in drug abusers cannot determine whether these reductions reflect the chronic exposure to the drug or the genetic differences or environmental influences that may have predisposed subjects to self-administer drugs. This question is relevant because one of the most challenging problems in the neurobiology of drug addiction is to understand why some individuals become addicted to drugs while others do not. Evidence from studies conducted in laboratory animals

implicates DA as one of the neurotransmitters that modulate the predisposition to drug self-administration (Piazza et al., 1991) and the DA D2 receptors as one of the targets that modulates a reinforcing response to drugs of abuse (Crabb & Phillips, 1998; De Wit & Wise, 1977; Maldonado et al., 1997). Because it was impractical to study the DA D2 receptor levels in subjects before and after they become addicted, we designed an experiment to investigate whether differences in levels of DA D2 receptors affect subjective hedonic responses to drugs in nonaddicted individuals.

For this purpose we measured the baseline levels of DA D2 receptors in the striatum in healthy non-drug-abusing subjects and in parallel assessed the behavioral responses to the stimulant drug MP (Volkow, Wang, Fowler, Logan, et al., 1999). Approximately half of the subjects described the effects of iv MP as pleasant and half as unpleasant. There were no differences in subjects' demographics, smoking status, or plasma MP concentration between individuals who liked and those that disliked MP. Subjects that described MP as pleasant had significantly lower levels of DA D2 receptors than did the subjects who described it as unpleasant. Moreover, D2 receptor levels correlated negatively with MP-induced pleasant effects ("happy" and "mood") and positively with its unpleasant effects ("annoyed" and "distrustful"). We recently replicated this finding in a different group of subjects in whom their baseline DA D2 receptors predicted self-reports for "drug liking" when given iv MP; the lower the receptors the higher the scores on drug liking (Volkow et al., 2002). The differences in response to MP between subjects with high and low D2 receptors could be explained if there is an optimal range for D2 receptor stimulation to be perceived as reinforcing; too little may not be sufficient but too much may be aversive. Thus, it is possible that in subjects with high D2 receptors a smaller dose of MP may have been perceived as pleasant. If D2 levels also modulate sensitivity to physiological reinforcers, then one could postulate that low D2 receptors would predispose a subject to use drugs as a means to compensate for the decreased activation of reward circuits. Alternatively it is possible either that low D2 receptors could predispose a person to psychostimulant abuse by favoring initial pleasant drug responses or that high D2 receptors may protect against drug abuse by favoring unpleasant drug responses. It is also likely that differences in the levels of DA release will affect the sensitivity of an individual to drugs of abuse and that DA receptors other than D2 will also contribute to the vulnerability toward drug consumption and abuse.

A limitation in the interpretation of these data is that they cannot corroborate a causal association between D2 receptor levels and a propensity to self-administer drugs. We therefore used the information from these clinical studies to design preclinical studies to test for causality (Thanos et al., 2001). We used an adenoviral vector to deliver the DA D2 receptor gene into the NAc of rats that had been previously trained to self-administer alcohol. This resulted in increases in DA D2 receptors that were within the range equivalent to that seen in humans ($\pm 50\%$) and in marked reductions in alcohol intake, which recovered as the DA D2 receptors returned to baseline levels. These results could be taken as indirect evidence of a protective role of high DA D2 receptor levels against drug abuse. Baseline levels of DA D2 receptors in the brain, which have been shown to be affected by environmental and social stressors (Papp et al., 1994, Morgan et al., 2002), provide a molecular mechanism that could explain the influence of the environment and genetics on a predisposition to drug abuse.

ROLE OF DA PATHWAYS IN LEARNING AND MEMORY IN ADDICTION

Considerable evidence exists regarding the role of DA in memory and learning (Castellano, Cestari, Cabib, & Puglisi-Allegra, 1991; Setlow and McGaugh, 1999). The role of DA in memory consolidation appears to be particularly important (Setlow & McGaugh, 1999). Neuronal studies of the firing patterns of DA cells when exposed to rewards and conditioned stimuli revealed patterns consistent with those observed during learning processes, which suggests that DA neurons facilitate associative learning (Waelti, Dickinson, & Schultz, 2001). Since drugs of abuse increase extracellular DA in limbic brain regions (including NAc) they will inherently facilitate the consolidation of the memory of the experience. Note that the NAc has been directly linked with associative learning for drug-related stimuli (Di Chiara, 1999). Moreover, cellular and molecular studies have pointed to the similar pathways involved with learning and memory and with drug addiction including long-term potentiation (LTP) and long-term depression (LTD) (Nestler, 2001). Indeed, some have advanced the argument that the chronic drug administration in addiction disrupts normal learning and memory systems, which in turn underlies maladaptive (compulsive) drug-seeking habits (Everitt, Dickinson, & Robbins, 2001). Multiple memory systems have been proposed to be involved in the process of drug addiction including conditioned incentive learning, habit learning, and declarative memory (reviewed in White, 1996). Conditioned incentive learning has been the memory system most investigated in addiction. Through conditioned learning, neutral stimuli coupled with the drug of abuse acquire reinforcing properties and motivational salience even in the absence of the drug. Both the amygdala and the NAc have been shown to be involved in conditioned learning (Brown, Robertson, & Fibiger, 1992; Di Chiara, 1999; Meil & See, 1997). Habit learning results in well-learned sequences of behavior that are elicited automatically by the appropriate stimuli. In this form of learning, stimulus–response associations are strengthened by the repeated presence of a stimulus followed by reinforcement. Both the caudate and the putamen are implicated in habit learning (White, 1996). Finally declarative memory, which is in part mediated by the hippocampus (Berke & Eichenbaum, 2001), has been related to the learning of affective states in relationship to drug intake. The relevance of the hippocampus in addiction is highlighted by a recent study showing that hippocampal stimulation can trigger relapse (Vorel, Liu, Hayes, Spector, & Gardner, 2001).

Memory systems are likely to be involved in the process of addiction via their influence on drug intoxication and craving. In drug intoxication, the previously learned drug experience will set the expectations of the drug effects in the drug abuser, which in turn will affect his or her response to the drug (Kirk, Doty, & De Wit, 1998; Mitchell, Laurent, & De Wit, 1996). Imaging studies during drug intoxication have revealed a distributed system of activation or deactivation that includes regions associated with learning of reward processes such as the NAc, hippocampus, and amygdala (Breiter et al., 1997; Stein et al., 1998). Drug craving is associated with the learned response that links the drug and its environment to a pleasurable or an intensely overpowering experience. The relevance these learned associations have on addiction is evidenced by the pernicious effect that a place, a person, or a cue—that brings back memories of the drug—have on the addict who is trying to stay clean. These trigger desire for the drug (craving) and not infrequently relapse. Imaging studies performed during craving induced by drug exposure, video, or

recall have demonstrated activation of brain regions implicated in several forms of memory. More specifically, activation has been reported in the amygdala (Breiter et al., 1999; Childress et al., 1999; Due, Huettel, Hall, & Rubin, 2002), (Grant et al., 1996; Kilts et al., 2001, Schneider et al., 1999), hippocampus (Kilts et al., 2001; Schneider et al., 2001), and dorsal striatum (Garavan et al., 2000; Volkow, Wang, Fowler, Hitzemann, et al., 1999).

However, the mesocortical DA circuit, which includes the prefrontal cortex, OFC, and CG, is also likely to be involved in addiction-related learned experiences through higher order top-down processes such as those involved in drug incentive salience and drug expectation or craving. Thus the circuits involved with memory-related aspects of addiction are likely to involve the frontal as well as limbic brain regions. Indeed the imaging studies of craving cited above have shown a complex pattern of activation that includes limbic, paralimbic, and striatal brain regions, but also the prefrontal cortex (Grant et al., 1996; Kilts et al., 2001). These brain regions interact with one another through associated circuits and are likely to affect the response to the drug. One could postulate that the activation of the hippocampus and amygdala in association with a drug-related context would activate the OFC and anterior CG in expectation of the reinforcer, which in turn would activate DA cells via fronto-mesencephalic connections (Karreman & Moghaddam, 1996), leading to a further increase in the salience of the drug and resultant craving. This interaction is dependent on memory circuits since knowledge of the strength of the stimulus as a reinforcer (in part through the hippocampus and amygdala) is a prerequisite of the attribution of salience to the drug or drug stimuli (in part through the OFC that assesses its relative value compared to that of simultaneously available reinforcers (Schultz et al., 2000)). Once the drug is consumed the increases in DA will further strengthen the memory and the motivational value of the drug and the drug-related stimuli.

ROLE OF THE FRONTAL CORTEX IN COGNITIVE BEHAVIORAL PROCESSES RELATED TO DRUG ADDICTION

From the studies performed on drug-addicted subjects it appears that the involvement of DA in addiction is in part mediated by its regulation of frontal cortical regions. In fact one of the most consistent findings from imaging studies is that of abnormalities in frontal cortical activity in drug-addicted subjects (reviewed Volkow et al. 2000). Therefore, one could expect that disruption of some of the higher cognitive and self-monitoring frontal cortical functions contributes to the process of addiction. Specifically, we propose that disruption of the frontal cortex leads to loss of self-directed and willed behaviors to automatic sensory-driven formulas and attribution of primary salience to the drug of abuse at the expense of other available rewarding stimuli. We hypothesized that these states are first evoked in the presence of the drug of abuse or cues conditioned to the drug but then become chronic action tendencies, contributing to relapse to binge (behavioral compulsion) and withdrawal-craving (mental compulsion, i.e., obsessive-ness), respectively (Goldstein & Volkow, 2002). The disruption of self-controlled behavior could be further accentuated during intoxication from prefrontal disinhibition of the amygdala (Rosenkranz & Grace, 2001). If a similar process occurs in the drug addicts during intoxication one could postulate that inhibition of prefrontal top-down processes (Miller & Cohen, 2001) would release behaviors that are normally kept under close

monitoring and simulate stress-like reactions in which inhibitory control is suspended and stimulus-driven behavior is accentuated.

The evidence of the involvement of the frontal cortex in cognitive processes pertaining to addiction (i.e., perception of response–reinforcement relations, response inhibition, and the expectation of reward) is mostly derived from imaging studies performed in non-drug-abusing subjects. Imaging studies on perception of response–reinforcement relations have used game-playing tasks with monetary payoffs (reviewed Breiter et al., 2001). Responses to gains and losses have been noted in the prefrontal cortex, OFC, anterior CG, and thalamus. The OFC appears to be activated mostly during conditions of uncertainty and under conditions that are dependent on feedback. The OFC is also activated by unpredictable reward (Berns et al., 2001).

The processing of emotionally salient and behaviorally adaptive information may be at the core of vigilant assessment of response–reinforcement relations. Indeed, the role of the frontal cortex, and specifically the anterior CG, in emotional processing has been demonstrated in several imaging studies. For example, the inferior frontal gyrus and dorsal anterior CG were shown to be involved in making a semantic, emotionally laden versus an orthographic decision in a verbal go/no-go task (Elliott, Rubinsztein, et al., 2000). The OFC and anterior CG have also been implicated in the experience of pleasant sensations (Francis et al., 1999) and in recognizing emotional facial expressions compared to neutral expressions (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). Taken together, the results of these studies suggest an important integrative role for the OFC and anterior CG in the analysis of the information that carries emotive, evaluative, and, in the long-term, survival significance for an individual, which offers a link to salience attribution.

Response inhibition is assumed to break down in periods of relapse and drug bingeing in drug-addicted subjects. Several imaging studies have confirmed the role of the OFC and the anterior CG in response inhibition in normal controls using the go/no-go task paradigm (including Casey et al., 1997) or the Stroop effect (including Carter et al., 2000). Better response inhibition was associated with a greater volume of activation in the OFC and a smaller magnitude of activation in the anterior CG, possibly implicating the OFC in the effort exerted when inhibiting a response and the anterior CG in error detection (Casey et al., 1997). The anterior CG has also been implicated in response competition and selection (Carter et al., 1998), both integral to inhibitory control. We have recently provided evidence for a change in the role of the OFC in response inhibition in addiction; whereas in addicted subjects greater baseline OFC activity was associated with lower conflict (higher Stroop interference score), in controls greater OFC metabolism was associated with higher conflict (lower Stroop interference score) (Goldstein et al., 2001).

Regarding the role of the frontal cortex in expectation, studies have demonstrated distinct brain regions and different response characteristics in anticipation of pain versus the experience of pain, with the former activating more anterior regions (including the anterior medial frontal cortex) than the latter (Ploghaus et al., 1999). Activation of the OFC has also been associated with expectation of other aversive stimuli including shock (Hugdahl et al., 1995).

CONCLUSION

Imaging studies have revealed marked disruptions of DA brain function in addicted subjects. This hypodopaminergic state may lead to deregulation of circuits involved with reward, motivation, memory, compulsion, judgment, and self-control. We postulate that the disruption of reward and motivational circuits would impair the motivational salience of natural reinforcers at the expense of drug-related stimuli, which then become the main motivational drive in the drug-addicted individual. The consolidated memories of the drug experiences strengthen the motivational salience and impair the ability to consolidate alternative memories with which to overcome the enhanced salience that the drug of abuse has on the addicted subject. In addition, disrupted DA activity is associated with the dysfunction of frontal cortical regions including the OFC and anterior CG, which could contribute to the compulsive self-administration and the lack of control (impaired inhibition) in addicted subjects and to disruptive cognitive operations that impair judgment and favor relapse.

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