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The Effects of Cocaine: A Shifting Target over the Course of Addiction

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Abstract

Repeated exposure to psychostimulant drugs such as cocaine has been shown in numerous studies to produce significant neuroadaptations in both structure and function throughout the brain. Nonhuman primate models provide a way to systematically evaluate these adaptations engendered by cocaine self-administration and simulate the progressive nature of cocaine addiction in humans. Functional activity, measured using the 2- $[^{14}\text{C}]$ deoxyglucose method, was evaluated at selected critical time points over the course of chronic cocaine self-administration in rhesus monkeys. The effects of cocaine exposure in the initial stages of self-administration resulted in changes in functional activity in a highly restricted network of interconnected brain regions when compared to activity in food-reinforced controls. This pattern of changes was confined mainly to ventromedial prefrontal cortex and ventral striatum. Following chronic exposure to cocaine self-administration, however, the spatial extent and intensity of significant alterations in functional activity expanded considerably. The shift in topography of these changes was orderly, originating ventromedially in the prefrontal cortical-ventral striatal network and expanding dorsally to encompass the dorsal striatum. A strikingly similar progression occurred within the cortical areas that project to each of these striatal regions. Preliminary studies suggest that this pattern is maintained despite periods of abstinence from cocaine. The shifting patterns of cerebral metabolic function that accompany longer durations of cocaine self-administration may underlie many of the characteristics of chronic drug exposure, and may provide transitional mechanisms to more compulsive cocaine use.

Keywords

prefrontal cortex; striatum; nonhuman primates; cocaine self-administration; cerebral glucose utilization; chronic drug exposure; abstinence

Introduction

Cocaine users are frequently characterized as suffering from a variety of cognitive impairments and affective dysfunction. Cognitively, these may include deficits in decision-making, abstract reasoning, and nonverbal problem solving (Hoff et al., 1996; Manschreck et al., 1990; Rogers and Robbins, 2001). In terms of affective dysfunction, cocaine users have a high incidence of

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depressive disorders, attention deficit disorder, and other psychopathologies (Carroll et al., 1994; Clure et al., 1999; Kilbey et al., 1992; Levin et al., 2007). Paralleling these alterations in affect and cognition, there are widespread structural and functional brain abnormalities associated with chronic cocaine use. Rates of cerebral metabolism assessed with PET, and changes in blood flow measured with fMRI and PET, are significantly lower in chronic cocaine users when compared to those of healthy control subjects, particularly in the prefrontal cortex and thalamus (Goldstein and Volkow, 2002; for review see Volkow et al., 2004). Furthermore, poor performance on response inhibition tasks (Goldstein et al., 2001; Kaufman et al., 2003) and working memory tasks (Hester and Garavan, 2004), both known to involve processing in prefrontal cortex, is associated with abnormal activation patterns in a network of cortical and subcortical areas including the caudate and thalamus, as well as cingulate, premotor, orbitofrontal, medial prefrontal, and insular cortices. Decreases in the structural integrity in prefrontal white matter (Lim et al., 2002) and gray matter density in distributed frontal and temporal cortical regions (Franklin et al., 2002) also occur in chronic cocaine users.

These studies of human drug addicts often imply or assume that cocaine exposure is the cause of these deficits. However, it is difficult to exclude the influence of other factors such as the use of other illegal and legal drugs, co-morbid psychiatric conditions, differences in lifestyle, etc. Further complications arise from the considerable differences across studies in inclusion criteria for drug use and abstinence, as well as the fact that self-reports of history and patterns of drug use in human subject are frequently unreliable and certainly highly variable. Perhaps most important, is the difficulty in assessing whether any of these changes occur as a result of drug exposure or pre-date any drug experiences. Because of these and many other problems, it is virtually impossible to isolate and address the issue of the consequences of chronic cocaine exposure in human populations. Therefore, one question remains largely unanswered: Does chronic cocaine use in and of itself have a major impact on brain activity? This is a central question, not only for treatment and recovery from addiction, but also for prevention as well.

Animal Models of Cocaine Exposure

One approach to addressing this question is the use of animal models to investigate the effects of repeated cocaine administration on behavioral, physiological and neurobiological endpoints. One of the goals of our research in recent years has been the development of an animal model that mimics the various stages of cocaine abuse. Thus, we have developed a nonhuman primate model of cocaine self-administration that enables us to predict the effects of cocaine exposure in humans by systematically manipulating variables and controlling for many of the problems encountered in human studies.

Nonhuman primates have been used in intravenous self-administration studies for nearly 40 years and have proved a valid and reliable model of human drug abuse (Griffiths et al., 1980; Johanson and Fischman, 1989; Mello and Negus, 1996). In addition, because monkeys have greater than 95% gene homology with humans (Hacia et al., 1998), they are more similar to humans in terms of phylogeny, anatomy, physiology and behavior than many other species. For example, nonhuman primates share considerable cytoarchitectural, neurochemical, and ultrastructural similarities with humans, particularly when considering the prefrontal cortex and basal ganglia (Carmichael and Price, 1994, 1996; Porrino and Lyons, 2000; Hardman et al., 2002). Furthermore, the connectivity patterns of the prefrontal cortex as well as other brain regions of nonhuman primates are highly homologous to those of humans (Ongur et al., 2003). Other advantages of nonhuman primates include similarities in the anatomy and physiology of dopaminergic (Gonzalez-Hernandez et al., 2004; Sanchez-Gonzalez et al., 2005) and noradrenergic systems (Smith et al., 2006), as well as the hypothalamic-pituitary-adrenal axis (Morgan et al., 2002). A final, important point must be made regarding behavior. Nonhuman primates can learn complex sequences of tasks that are more applicable to modeling

the human drug-seeking condition as compared to the limited behavioral repertoires of rodent species. Furthermore, because they can perform higher order cognitive tasks, they may provide insights into the psychiatric and psychological deficits observed in human drug users. Because of these and other similarities, nonhuman primates can be powerful animal models of many aspects of human drug abuse.

Cocaine abuse progresses through a number of temporal stages that begin with initial experimentation, advance through casual use, and finally progress to addiction. Reports by cocaine users portray their initial experience with cocaine as highly pleasurable. Cocaine may induce intense feelings of euphoria and well-being, along with an intensification of emotions and sexual feelings (Gawin 1991; Johanson and Fischman, 1989). When drug use continues, the patterns of consumption shift from casual, occasional use to higher-dose, sometimes long duration binges, where users re-administer cocaine as often as every 10 to 30 minutes for as long as 24 hours (Gawin, 1991). These binges are at times accompanied by intense feelings of craving and a decreased sensitivity to the negative effects of the drug (Gawin, 1991, 1993). With continued high intensity use and bingeing, however, reports of panic attacks, paranoia, and intense anxiety are frequent (Post and Weiss, 1988). The overall goal of our studies has been to model these stages of drug use in the progression to addiction, in order to examine the nature of the changes within the central nervous system that occur as brain systems adapt to, and compensate for, cocaine use and the cessation of its use. The basic premise of this work has been that because of the many structural neuroadaptations that develop throughout the course of chronic drug use, it is likely that cocaine will have a very different set of functional effects at each stage of this process.

Brain Imaging Methods

Although we have studied a number of systems, our current comments are confined to studies of functional brain activity as reflected by the measurement of rates of local cerebral glucose utilization with the 2- $[^{14}\text{C}]$ deoxyglucose method (2DG). Because cocaine acts at dopaminergic, noradrenergic, and serotonergic transporters, as well as functioning as a local anesthetic, its effects are unlikely to be confined to a single action at a single site. Instead, the response to the administration of cocaine is more likely to result from multiple actions, at both central and peripheral sites. These actions depend not only on the dose and route of administration of the drug, but also on the environmental context (Robinson et al., 1998), physiological status of the organism, and most importantly for the purposes of the present discussion, on the history of previous exposure to cocaine and other drugs (Ellinwood and Kilbey, 1980; Post and Contel, 1981). Therefore, to characterize fully the neural substrates of the actions of a drug such as cocaine, it is necessary to identify neural events in networks of interconnected areas, not merely at a single location.

Imaging methods such as metabolic mapping with 2DG were developed to investigate changes in biochemical processes throughout the entire brain simultaneously. The 2DG method measures rates of cerebral glucose utilization with quantitative autoradiography in neuroanatomically defined areas of the brains of conscious, behaving organisms. The rate of glucose metabolism is a measure of the energy used, which in turn is a reflection of the amount of work done within a given brain region. In the brain, therefore, where work is electrical or chemical, this is quantifiable as functional activity. There are a number of advantages of this approach beyond the ability to visualize the entire brain simultaneously. Glucose utilization can be measured in conscious, behaving animals either during, or at any given time-point after experimental manipulations, allowing direct quantification of the effects of that manipulation on brain activity. Although the 2DG method does not permit repeated testing in the same animal over time, the use of autoradiography provides a high degree of spatial resolution, enabling the

investigation of small regions or sub-regions of the brain, and making possible the visualization of subtle patterns of changes in functional activity across the entire brain.

Cocaine self-administration paradigms

For all of our studies, adult male rhesus monkeys were initially trained to respond for banana pellets on a fixed-interval 3 minute (FI-3) schedule of reinforcement. Sessions ended after 30 food presentations and were followed by retraction of the levers and extinguishing of all stimulus and house lights. Animals remained in the experimental chambers for an additional 30 minutes before being returned to their home cages. After baseline performance was established, all animals were surgically implanted with venous catheters. Performance of control animals (n=6) was maintained by food reinforcement, whereas cocaine (0.3 mg/kg/injection) was substituted for food in self-administration monkeys. This dose, while on the descending limb of the dose response curve (Nader et al., 1999), is more reinforcing than lower doses and more likely to produce the persistent effects on brain structure and function than lower doses, thereby better modeling the conditions of human drug abuse. For all groups, responding was maintained under an FI-3 min schedule and sessions ended after 30 reinforcer presentations. Sessions were conducted daily and continued for 5 (n=4) or 100 (n=4) days. Metabolic mapping took place immediately *after* the last infusion of the final session of cocaine or food self-administration. The measurement of functional activity at this time-point eliminated the confound of different response rates of individual animals during the experimental sessions, as well as the presence of any anticipatory or expectancy effects that may have been present had the 2DG procedure taken place during or prior to self-administration sessions. This is a critical detail because it ensures that differences in functional activity between food and cocaine reinforced groups are due to the effects of cocaine alone, and are not the result of other behaviors. For further details of the procedures and behavioral outcomes, see Nader et al., 2002.

In our first series of experiments, the effects of cocaine were evaluated following 5 sessions of cocaine self-administration (Porrino et al., 2002). Total intake was 45 mg/kg (30 injections per session). Five days of self-administration was chosen to model the initial phases of drug exposure when cocaine use is still considered casual or recreational, well before any transition to addiction has occurred. Five days also represents a time point just after the acquisition of self-administration behavior at which cocaine is clearly acting as a reinforcer, but is prior to the advent of significant biological and behavioral adaptations.

A second set of studies examined the effects of repeated exposure to cocaine, evaluating changes in the response to cocaine after 100 days of daily cocaine self-administration (Beveridge et al., 2006). In these studies, monkeys self-administered 0.3 mg/kg/injection cocaine (30 injections per session) and had administered 900 mg/kg by the completion of 100 daily sessions. Control monkeys responded for food on the same schedule for the same duration of time. This time point was chosen in an attempt to model the effects of repeated cocaine, and to evaluate the changes in the way in which the brain responded to the continued chronic cocaine exposure.

In both sets of studies, the alterations in functional activity which were observed represent the combination of the acute effects of self-administered cocaine during the final session along with the effects of previous experience of cocaine self-administration. In other words, the changes in glucose metabolism are in response to acute cocaine following either short-term or chronic exposure to cocaine self-administration; the difference being the duration of cocaine exposure. The amount of drug self-administered during each session was kept constant across both sessions and animals. Although there are limitations to this approach, especially with

respect to evaluating individual differences in behavior, any variations in the metabolic response can be directly attributed to the cocaine history.

Initial Exposure

With only 5 days of experience with cocaine self-administration, the effects of cocaine resulted in significant alterations in functional activity, as reflected by rates of glucose utilization, in a highly restricted network of interconnected brain regions when compared to activity in food-reinforced controls. This pattern of change was predominantly limbic in nature, confined mainly to ventromedial prefrontal cortex and ventral striatum (Porrino et al., 2002).

Within the prefrontal cortex, a detailed analysis of the decreases in functional activity using the cytoarchitectural boundaries described by Carmichael and Price (Carmichael and Price, 1994, 1996) showed that changes were concentrated along the medial wall in areas 32, 25, 14 and 24, as well within the orbitofrontal cortex in area 13 rostrally and areas Iam and Ial more caudally (see Fig. 1 top panels). These regions comprise portions of both the medial and orbital networks identified by Carmichael and Price. The medial network, represented here by structures along the medial wall, is thought to modulate visceral function and has strong connections to hypothalamus and brainstem. In contrast, the orbital network, which includes the aforementioned orbitofrontal cortical areas, integrates activity from sensory modalities such as smell and taste (Rolls, 1997, 2000) and has been implicated in functions such as decision making (Bechara et al., 2000) and response inhibition (Roberts and Wallis, 2000). Both networks project to ventral and dorsomedial striatum (Haber et al., 2006). Cocaine then, even with minimal self-administration exposure, can alter functional activity in those portions of prefrontal cortex involved in the processing and expectation of reward related stimuli, as well as the modification of visceral reactions to them. These portions of prefrontal cortex project to ventral and medial striatum where cocaine also profoundly alters functional activity.

Within the striatum, significant decreases in glucose utilization following initial cocaine exposure were evident in the ventral striatum, including both the shell and core of the nucleus accumbens (Fig. 2 upper panel and lower panel Fig. 3). These alterations were most intense in the posterior portions of the ventral striatum just rostral to the anterior commissure. Though decreases in metabolism similar to those in the ventral striatum were also observed in the more medial and ventral portions of the caudate, these were again mainly concentrated just rostral to the anterior commissure (see Fig. 3, upper panel). As the ventral striatum is predominantly limbic in function, the early phase of cocaine administration appears to impact the portions of the striatum involved in the processing of reward and motivational information, with smaller or no effects in other functional domains.

The initial stages of experience with cocaine, then, influence a limited network of brain regions comprised largely of limbic prefrontal cortex and its projection fields in the ventral striatum. This circuitry participates in the guidance of reward-related behaviors such as feeding, while dysfunction of this circuitry has been implicated in depression, anhedonia, impaired decision making, and addiction (Bechara, 1994; Franklin et al., 2002; Goldstein and Volkow, 2002; Grant et al., 2000; Kelley, 2005; Nugent et al., 2006; Robbins, 2007; Rogers and Robbins, 2001).

Chronic Exposure

In contrast to the limited effects of initial cocaine self-administration, following 100 days of chronic cocaine self-administration, the topography and intensity of significant reductions in functional activity expanded considerably. Instead of the highly restricted pattern of functional brain changes observed early in the course of drug exposure, after continued exposure to self-administration over several months cocaine produced widespread alterations in functional

activity. This expansion of effects included structures not previously impacted by cocaine including the amygdala, hippocampus, temporal and parietal cortex, as well as areas previously affected by cocaine at the earlier time point, including the striatum and prefrontal cortex (Porrino et al., 2004; Beveridge et al., 2006).

In the case of the prefrontal cortex, there was considerable overlap in the patterns of changes in functional activity when comparing the initial and chronic stages of cocaine self-administration. This was particularly evident along regions of the medial wall of the prefrontal cortex (areas 24, 14, 32 and 25). Although the spatial extent of the changes in these regions was similar, the longer histories of cocaine exposure resulted in effects of greater magnitude. Furthermore, the response to cocaine broadened across the orbital surface to include not only area 13, which had been impacted by 5 days of self-administration, but also area 11 and some of area 12. This shift can be seen in Fig. 1 by comparing the upper panel which depicts the changes in cerebral metabolism in the initial phases of self-administration to the lower panel which depicts the changes after longer exposure periods. Finally, with more prolonged cocaine self-administration experience the reductions tended to spread more rostrally to encompass area 10 of the frontal pole. It appears, then, that the effects of cocaine in prefrontal cortex may continue to grow in both magnitude and spatial extent with repeated exposure, suggesting a larger influence of cocaine in areas mediating the processing of reward-related and emotional stimuli, as well as an expansion into areas involved in higher order cognitive processing.

A similar picture emerged in the striatum. Rates of metabolism in the ventral striatum core and shell were significantly decreased at all pre-commissural levels following chronic exposure. This can be seen in the lower panel of Fig. 3. However, in the dorsal striatum, the pattern of changes in functional activity was considerably different. In contrast to the initial phases of self-administration, where reductions in cerebral metabolism were confined to the more ventromedial portions of the caudate and putamen just rostral to the anterior commissure (see Fig. 2), with extended experience cerebral metabolism was reduced throughout both caudate and putamen rostral to the anterior commissure even in their most anterior aspects. In addition, the decreases extended into the post-commissural striatum (Fig. 2 and 3 upper panel). Clearly then, the impact of cocaine on rates of cerebral metabolism in the striatum expand dramatically with increased exposure to cocaine. This suggests that the impact of cocaine impinges progressively into areas of the striatum involved in the processing of cognitive and sensorimotor information as cocaine use continues.

This shift in the pattern of alterations in glucose utilization as a result of chronic exposure is also consistent with reports of adaptations in dopamine and opioid systems. Prolonged self-administration results in an upregulation in these monkeys of dopamine transporter binding sites (Letchworth et al., 2001) and preprodynorphin mRNA (Fagergren et al., 2003), as well as downregulation of D₂ receptors (Moore et al., 1998; Nader et al., 2002). The pattern of these adaptations followed an identical progression from ventral to dorsal striatum, as well as an expansion to more rostral and caudal portions of the striatum with increasing durations of cocaine self-administration history. Again, taken together, it is clear that adaptations associated with cocaine exposure continue to expand over time and are likely to involve more and more of the behavioral repertoire.

Recently, hypotheses concerning the development of addiction have centered on the progressively habitual or compulsive nature of drug use, with the concept that control over drug use evolves from action to habit (Berke and Hyman, 2000; Everitt and Wolf, 2002). More specifically, it is thought that a shift in control from ventral to dorsal striatal domains is in part responsible for the progression from voluntary drug use to more habitual and compulsive use (Everitt and Robbins, 2005). Our data concerning the expanding effects of cocaine with progressively longer durations of self-administration experience provide a neurobiological

framework for these behavioral and cognitive concepts. In particular the expansion of cocaine's effects in the functional domains of the striatum moving from primarily motivational, ventral limbic areas to more dorsal habit-related regions perhaps provides an anatomical basis for the behavioral shift that may occur in human addicts.

Abstinence

More recent studies from our laboratory have focused on the question of the persistence of the effects of cocaine on cerebral metabolism that result after a history of chronic self-administration. How does the functional response change as a result of the cessation of drug use and subsequent re-exposure to cocaine? Our original hypothesis was that the functional response to cocaine would be diminished following abstinence and that the pattern of functional activity would more closely resemble that observed in the initial stages of cocaine self-administration. Another possibility, however, is that the adaptations to the discontinuation of drug use develop that further alter the response to cocaine after re-exposure. Finally, the neuroadaptations underlying cocaine's effects after chronic exposure may be permanent, resulting in no change in the functional response to cocaine despite extended periods of abstinence. In these studies, adult male monkeys self-administered cocaine for 100 days as described previously, followed by one month of abstinence ($n=3$). At the end of the abstinence period, animals were given the opportunity to self-administer cocaine in a final session after which the metabolic mapping procedure was applied, again as in our previous studies described above.

Although these data are highly preliminary, one month of abstinence did not appear to have significantly diminished the response to cocaine self-administration as originally predicted. In the striatum, for example in the small group of animals studied to date, cocaine produced significant decreases in glucose utilization in both the core and shell of the ventral striatum, which were essentially identical in magnitude and spatial extent as those seen after chronic self-administration history, regardless of the abstinence period. This is shown in the lower panel of Fig. 3. In the dorsal striatum, cocaine also produced similar effects (Fig. 3, upper panel). These data suggest that the neuroadaptations associated with chronic cocaine exposure are robust and persistent. If these data are confirmed in subsequent studies, they suggest that the alterations in brain function produced by cocaine may be resistant to reversal by a simple regime of abstinence and pharmacological or behavioral interventions are necessary for recovery to occur.

Conclusions

Our studies were originally designed to characterize the structural and functional changes in the brain that accompany various stages of cocaine addiction and abstinence using a nonhuman primate model of cocaine self-administration. These studies combined the use of 1) nonhuman primates with homologous anatomy to humans, 2) cocaine self-administration rather than non-contingent drug administration, 3) prolonged drug exposure of longer than 3 months, and 4) the high spatial resolution of detailed autoradiographical analyses. Together, these elements have provided unique insights into the consequences of cocaine use.

One important outcome of this series of studies was the finding that exposure to cocaine in and of itself can produce significant dysregulation in neurotransmitter systems and adaptations in the functional response to cocaine (Lyons et al., 1996; Porrino et al., 2002). These changes include increases in the density of norepinephrine (Beveridge et al., 2005) and dopamine transporters (Letchworth et al., 2001), increases in dopamine D1 receptors (Nader et al., 2002), as well as decreases in the concentration of dopamine D2 receptors (Nader et al., 2002). These alterations in brain structure and function can be directly attributable to the effects

of cocaine, unlike studies of human addicts in which differences between users and control populations could result from a number of factors besides cocaine exposure, including co-morbid psychiatric disorders, use of other legal and illegal drugs, or pre-existing differences.

It is challenging to attempt to extrapolate these findings directly to human drug abusers. To date, there have been very few investigations of the functional consequences of acute cocaine administration to humans with current imaging methods. One study that used PET to measure glucose metabolism in non-treatment seeking cocaine users found that following the non-contingent intravenous administration of cocaine, rates of cerebral metabolism were reduced throughout the brain including neocortex, basal ganglia, thalamus and midbrain (London et al., 1990). These findings are consistent with the present reductions described here after chronic exposure. However, other investigators using fMRI found increased signal in many of these same areas (Breiter et al, 1997). Although these differences might be methodological in nature, a more recent study by Risinger and colleagues (2005) suggests an alternative explanation. These investigators examined the effects of cocaine self-administration during an fMRI session. In contrast to the previous study of non-contingent drug administration, feelings of rush and high after self-administration were highly correlated with decreased activity in the ventral striatum, medial and ventral prefrontal cortex including the cingulate gyrus, as well as portions of the temporal cortex (Risinger et al., 2005). By using self-administration, this study was able to overcome many of the problems inherent in laboratory investigations of the effects of drug in humans where an unfamiliar and artificial lab setting in combination with unknown drug paraphernalia and administration can obscure the drug experience. These data closely parallel the findings in the nonhuman primate model of self-administration used in the studies reviewed here and underscore the importance of the context of drug administration as an important determinant of its effects.

Another key contribution of these studies is the characterization of the progression in the functional response to cocaine with increasing drug experience as following a clear and definable pattern. The shift in topography of these changes is orderly, originating ventromedially in the prefrontal cortical-ventral striatal network and expanding dorsally to encompass the dorsal striatum, as well as its rostral and caudal extents. A strikingly similar progression occurs within the cortical areas that project to each of these striatal regions. The complex organization of striato-nigro-striatal circuitry, as recently described by Haber and colleagues (2000) provides an anatomical framework through which information flow between striatal regions could be achieved. They have shown that connections between adjacent striatal regions are arranged in a series of ascending spiraling loops through the ventral midbrain. This hierarchical arrangement, perhaps, underlies the manner in which the pattern of afferents to the striatum determines the functional response to cocaine, and explains how this response expands with increasing durations of exposure. In addition, functional activity in the striatum is also directly influenced by input from the cortex (Brown et al., 1998). Reciprocal and non-reciprocal cortico-thalamic connections (McFarland and Haber, 2000) may further amplify the impact of cocaine on the cortex, and in turn the striatal circuits to which these areas project. In summary then, one of the hallmark features of the addiction process is the growing importance of substances of abuse in an individual's life, and the expanding effects of cocaine described here may be the neurobiological basis for this characteristic of addiction.

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References

- Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50:7–15. [PubMed: 8039375]

- Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 2000;10:295–307. [PubMed: 10731224]
- Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* 2000;25:515–532. [PubMed: 10774721]
- Beveridge TJ, Smith HR, Daunais JB, Nader MA, Porrino LJ. Chronic cocaine self-administration is associated with altered functional activity in the temporal lobes of non human primates. *Eur J Neurosci* 2006;23:3109–3118. [PubMed: 16820001]
- Beveridge TJ, Smith HR, Nader MA, Porrino LJ. Effects of chronic cocaine self-administration on norepinephrine transporters in the nonhuman primate brain. *Psychopharmacology (Berl)* 2005;180:781–788. [PubMed: 15739079]
- Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, et al. Acute effects of cocaine on human brain activity and emotion. *Neuron* 1997;19:591–611. [PubMed: 9331351]
- Brown LL, Smith DM, Goldbloom LM. Organizing principles of cortical integration in the rat neostriatum: corticostriate map of the body surface is an ordered lattice of curved laminae and radial points. *J Comp Neurol* 1998;392:468–488. [PubMed: 9514511]
- Carmichael ST, Price JL. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *J Comp Neurol* 1994;346:366–402. [PubMed: 7527805]
- Carmichael ST, Price JL. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *J Comp Neurol* 1996;371:179–207. [PubMed: 8835726]
- Carroll KM, Rounsaville BJ, Gordon LT, Nich C, Jatlow P, Bisighini RM, et al. Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry* 1994;51:177–187. [PubMed: 8122955]
- Clure C, Brady KT, Saladin ME, Johnson D, Waid R, Rittenbury M. Attention-deficit/hyperactivity disorder and substance use: symptom pattern and drug choice. *Am J Drug Alcohol Abuse* 1999;25:441–448. [PubMed: 10473007]
- Ellinwood EH Jr, Kilbey MM. Fundamental mechanisms underlying altered behavior following chronic administration of psychomotor stimulants. *Biol Psychiatry* 1980;15:749–757. [PubMed: 6106515]
- Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005;8:1481–1489. [PubMed: 16251991]
- Everitt BJ, Wolf ME. Psychomotor stimulant addiction: a neural systems perspective. *J Neurosci* 2002;22:3312–3320. [PubMed: 11978805]
- Fagergren P, Smith HR, Daunais JB, Nader MA, Porrino LJ, Hurd YL. Temporal upregulation of prodynorphin mRNA in the primate striatum after cocaine self-administration. *Eur J Neurosci* 2003;17:2212–2218. [PubMed: 12786988]
- Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, et al. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry* 2002;51:134–142. [PubMed: 11822992]
- Gawin FH. Cocaine addiction: psychology and neurophysiology. *Science* 1991;251:1580–1586. [PubMed: 2011738]
- Gawin, FH. Cocaine addiction: psychology, neurophysiology and treatment. Oxford University Press; New York: 1993.
- Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 2002;159:1642–1652. [PubMed: 12359667]
- Goldstein RZ, Volkow ND, Wang GJ, Fowler JS, Rajaram S. Addiction changes orbitofrontal gyrus function: involvement in response inhibition. *Neuroreport* 2001;12:2595–2599. [PubMed: 11496155]
- Gonzalez-Hernandez T, Barroso-Chinea P, De La Cruz Muros I, Del Mar Perez-Delgado M, Rodriguez M. Expression of dopamine and vesicular monoamine transporters and differential vulnerability of mesostriatal dopaminergic neurons. *J Comp Neurol* 2004;479:198–215. [PubMed: 15452855]
- Grant S, Contoreggi C, London ED. Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia* 2000;38:1180–1187. [PubMed: 10838152]
- Griffiths, RR.; Bigelow, GE.; Henningfield, JE. Similarities in animals and human drug-taking behavior. JAI Press; Greenwich, CT: 1980.

- Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 2000;20:2369–2382. [PubMed: 10704511]
- Haber SN, Kim KS, Maily P, Calzavara R. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. *J Neurosci* 2006;26:8368–8376. [PubMed: 16899732]
- Hacia JG, Makalowski W, Edgemon K, Erdos MR, Robbins CM, Fodor SP, et al. Evolutionary sequence comparisons using high-density oligonucleotide arrays. *Nat Genet* 1998;18:155–158. [PubMed: 9462745]
- Hardman CD, Henderson JM, Finkelstein DI, Horne MK, Paxinos G, Halliday GM. Comparison of the basal ganglia in rats, marmosets, macaques, baboons, and humans: volume and neuronal number for the output, internal relay, and striatal modulating nuclei. *J Comp Neurol* 2002;445:238–255. [PubMed: 11920704]
- Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. *J Neurosci* 2004;24:11017–11022. [PubMed: 15590917]
- Hoff AL, Riordan H, Morris L, Cestaro V, Wieneke M, Alpert R, et al. Effects of crack cocaine on neurocognitive function. *Psychiatry Res* 1996;60:167–176. [PubMed: 8723307]
- Johanson CE, Fischman MW. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989;41:3–52. [PubMed: 2682679]
- Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci* 2003;23:7839–7843. [PubMed: 12944513]
- Kelley AE, Schiltz CA, Landry CF. Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. *Physiol Behav* 2005;86:11–14. [PubMed: 16139315]
- Kilbey MM, Breslau N, Andreski P. Cocaine use and dependence in young adults: associated psychiatric disorders and personality traits. *Drug Alcohol Depend* 1992;29:283–290. [PubMed: 1559435]
- Letchworth SR, Nader MA, Smith HR, Friedman DP, Porrino LJ. Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys. *J Neurosci* 2001;21:2799–2807. [PubMed: 11306632]
- Levin FR, Bisaga A, Raby W, Aharonovich E, Rubin E, Mariani J, et al. Effects of major depressive disorder and attention-deficit/hyperactivity disorder on the outcome of treatment for cocaine dependence. *J Subst Abuse Treat*. 2007in press
- Lim KO, Choi SJ, Pomara N, Wolkin A, Rotrosen JP. Reduced frontal white matter integrity in cocaine dependence: a controlled diffusion tensor imaging study. *Biol Psychiatry* 2002;51:890–895. [PubMed: 12022962]
- London ED, Cascella NG, Wong DF, Phillips RL, Dannals RF, Links JM, et al. Cocaine-induced reduction of glucose utilization in human brain. A study using positron emission tomography and [fluorine 18]-fluorodeoxyglucose. *Arch Gen Psychiatry* 1990;47:567–574. [PubMed: 2350209]
- Lyons D, Friedman DP, Nader MA, Porrino LJ. Cocaine alters cerebral metabolism within the ventral striatum and limbic cortex of monkeys. *J Neurosci* 1996;16:1230–1238. [PubMed: 8558251]
- Manschreck TC, Schneyer ML, Weisstein CC, Laughery J, Rosenthal J, Celada T, et al. Freebase cocaine and memory. *Compr Psychiatry* 1990;31:369–375. [PubMed: 2387150]
- McFarland NR, Haber SN. Convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum in the primate. *J Neurosci* 2000;20:3798–3813. [PubMed: 10804220]
- Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. *Neuropsychopharmacology* 1996;14:375–424. [PubMed: 8726752]
- Moore RJ, Vinsant SL, Nader MA, Porrino LJ, Friedman DP. Effect of cocaine self-administration on dopamine D2 receptors in rhesus monkeys. *Synapse* 1998;30:88–96. [PubMed: 9704885]
- Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, et al. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. *Nat Neurosci* 2002;5:169–174. [PubMed: 11802171]
- Nader MA, Daunais JB, Moore T, Nader SH, Moore RJ, Smith HR, et al. Effects of cocaine self-administration on striatal dopamine systems in rhesus monkeys: initial and chronic exposure. *Neuropsychopharmacology* 2002;27:35–46. [PubMed: 12062905]

- Nader MA, Green KL, Luedtke RR, Mach RH. The effects of benzamide analogues on cocaine self-administration in rhesus monkeys. *Psychopharmacology (Berl)* 1999;147:143–152. [PubMed: 10591881]
- Nugent AC, Milham MP, Bain EE, Mah L, Cannon DM, Marrett S, et al. Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. *Neuroimage* 2006;30:485–497. [PubMed: 16256376]
- Ongur D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol* 2003;460:425–449. [PubMed: 12692859]
- Paxinos, G.; Huang, XF.; Toga, AW. The rhesus monkey brain in stereotaxic coordinates. Academic Press; San Diego, CA: 2000.
- Porrino LJ, Lyons D. Orbital and medial prefrontal cortex and psychostimulant abuse: studies in animal models. *Cereb Cortex* 2000;10:326–333. [PubMed: 10731227]
- Porrino LJ, Lyons D, Miller MD, Smith HR, Friedman DP, Daunais JB, et al. Metabolic mapping of the effects of cocaine during the initial phases of self-administration in the nonhuman primate. *J Neurosci* 2002;22:7687–7694. [PubMed: 12196592]
- Porrino LJ, Lyons D, Smith HR, Daunais JB, Nader MA. Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. *J Neurosci* 2004;24:3554–3562. [PubMed: 15071103]
- Post, RM.; Contel, NR. Cocaine-induced behavioral sensitization: a model for recurrent manic illness. Elsevier; Amsterdam: 1981.
- Post RM, Weiss SR. Psychomotor stimulant vs. local anesthetic effects of cocaine: role of behavioral sensitization and kindling. *NIDA Res Monogr* 1988;88:217–238. [PubMed: 2905429]
- Risinger RC, Salmeron BJ, Ross TJ, Amen SL, Sanfilippo M, Hoffmann RG, et al. Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. *Neuroimage* 2005;26:1097–1108. [PubMed: 15886020]
- Robbins TW. Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Philos Trans R Soc Lond B Biol Sci* 2007;362:917–932. [PubMed: 17412678]
- Roberts AC, Wallis JD. Inhibitory control and affective processing in the prefrontal cortex: neuropsychological studies in the common marmoset. *Cereb Cortex* 2000;10:252–262. [PubMed: 10731220]
- Robinson TE, Browman KE, Crombag HS, Badiani A. Modulation of the induction or expression of psychostimulant sensitization by the circumstances surrounding drug administration. *Neurosci Biobehav Rev* 1998;22:347–354. [PubMed: 9579324]
- Rogers RD, Robbins TW. Investigating the neurocognitive deficits associated with chronic drug misuse. *Curr Opin Neurobiol* 2001;11:250–257. [PubMed: 11301247]
- Rolls ET. Taste and olfactory processing in the brain and its relation to the control of eating. *Crit Rev Neurobiol* 1997;11:263–287. [PubMed: 9336714]
- Rolls ET. The orbitofrontal cortex and reward. *Cereb Cortex* 2000;10:284–294. [PubMed: 10731223]
- Sanchez-Gonzalez MA, Garcia-Cabezas MA, Rico B, Cavada C. The primate thalamus is a key target for brain dopamine. *J Neurosci* 2005;25:6076–6083. [PubMed: 15987937]
- Smith HR, Beveridge TJ, Porrino LJ. Distribution of norepinephrine transporters in the non-human primate brain. *Neuroscience* 2006;138:703–714. [PubMed: 16427744]
- Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology* 2004;47(Suppl 1):3–13. [PubMed: 15464121]

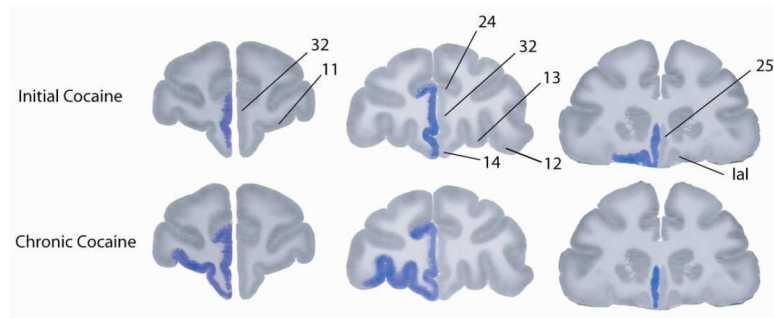


Figure 1.

Areas of cerebral metabolic response produced by self-administered cocaine in the prefrontal cortex of rhesus monkey. Shown are representative autoradiograms of 2- $[^{14}\text{C}]$ deoxyglucose uptake in coronal sections through rostral to caudal levels of prefrontal cortex (+ 15.30, + 9.5 and + 4.5 from bregma; Paxinos et al., 2000). Top panel shows the effects of initial (5 days) cocaine self-administration, bottom panel shows the effects of chronic (100 days) cocaine self-administration. Blue coloring superimposed upon the grayscale autoradiograms represents the location of significant decreases in rates of glucose utilization (note that effects were bilateral, however in the interest of simplicity the effects are depicted on one hemisphere). Numbered labels are from Brodmann's definitions of cortical areas.

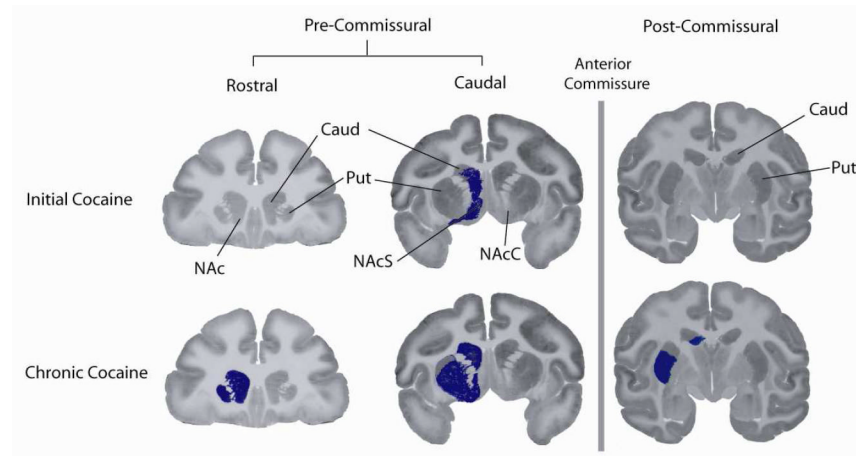


Figure 2.

Areas of cerebral metabolic response produced by self-administered cocaine in the striatum of rhesus monkey. Shown are representative autoradiograms of 2-[^{14}C]deoxyglucose uptake in coronal sections of rostral and caudal pre-commissural and post-commissural striatum (+ 4.50, - 0.45 and - 9.0 from bregma respectively; Paxinos et al., 2000). Top panel are effects of initial (5 days) cocaine self-administration, bottom panel are effects of chronic (100 days) cocaine self-administration. The vertical line represents the level of the anterior commissure. Blue coloring superimposed upon the grayscale autoradiograms represents the location of significant decreases in rates of glucose utilization (note that effects were bilateral, however in the interest of simplicity the effects are depicted on one hemisphere). Caud, caudate; Put, putamen; NAc, rostral nucleus accumbens; NAcC, nucleus accumbens core; NAcS, nucleus accumbens shell.

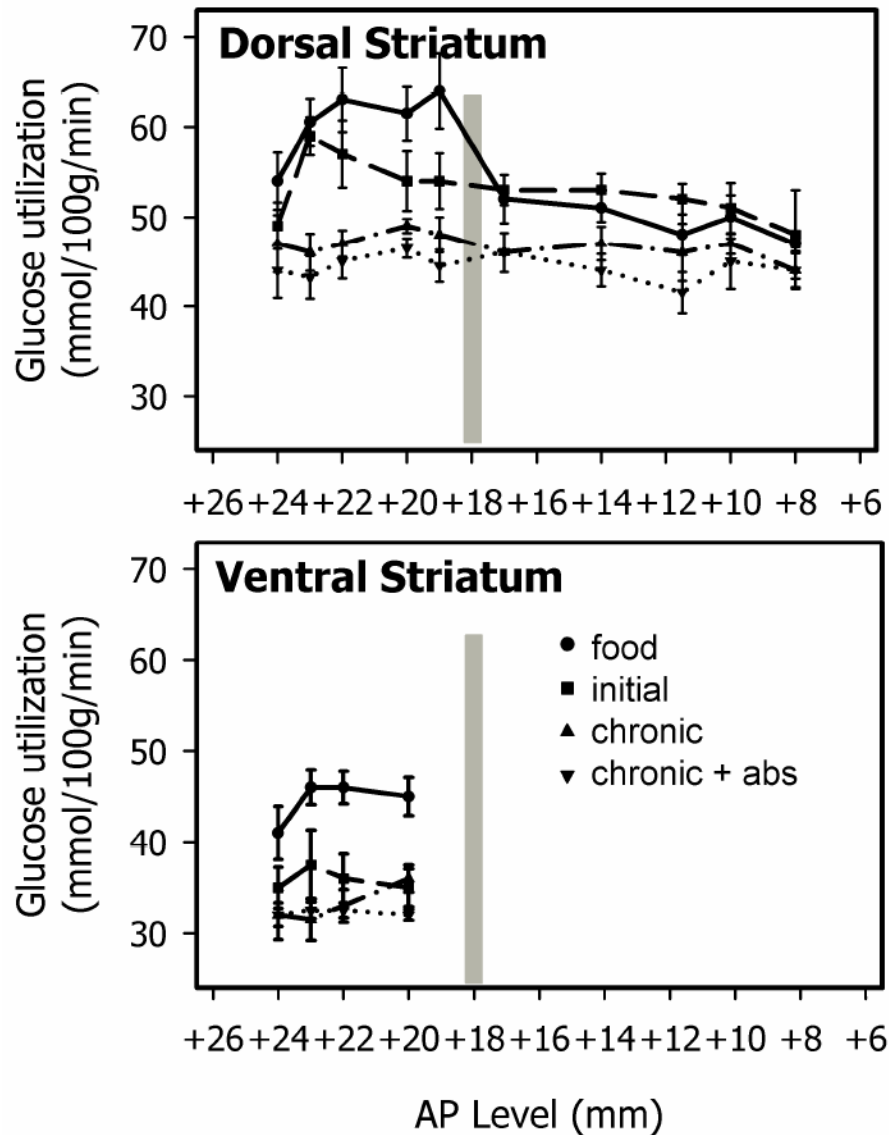


Figure 3.

The effects of cocaine self-administration on rates of local cerebral glucose utilization across the anterior-posterior extent of the dorsal (upper panel) and ventral (lower panel) striatum of rhesus monkey. Rates of glucose utilization of monkeys in the initial (5 day), chronic (100 day) and abstinent (100 day self-administration with 30 days abstinence) stages of self-administration are compared with rates of glucose utilization of control monkeys in which responding was maintained by food under identical schedules of reinforcement. The vertical line in each panel represents the level of the anterior commissure.