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The role of orbitofrontal cortex in drug addiction: a review of preclinical studies

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Abstract

Studies using brain imaging methods have shown that neuronal activity in the orbitofrontal cortex, a brain area thought to promote the ability to control behavior according to likely outcomes or consequences, is altered in drug addicts. These human imaging findings have led to the hypothesis that core features of addiction like compulsive drug use and drug relapse are mediated in part by drug-induced changes in orbitofrontal function. Here, we discuss results from laboratory studies using rats and monkeys on the effect of drug exposure on orbitofrontal-mediated learning tasks and on neuronal structure and activity in orbitofrontal cortex. We also discuss results from studies on the role of the orbitofrontal cortex in drug self-administration and relapse. Our main conclusion is that while there is clear evidence that drug exposure impairs orbitofrontal-dependent learning tasks and alters neuronal activity in orbitofrontal cortex, the precise role these changes play in compulsive drug use and relapse has not yet been established.

Keywords

drug cues; orbitofrontal cortex; reinstatement; relapse; reversal learning; stress

Introduction

Drug addiction is characterized by compulsive drug-seeking and high frequency of relapse to drug use [1-3]. For decades, basic research on drug addiction has been largely devoted to understanding the mechanisms underlying the acute rewarding effects of drugs [4]. This research indicates that the mesolimbic dopamine system and its efferent and afferent connections is the neural substrate for the rewarding effects of drugs of abuse [4-7]. In recent years, however, it has become clear that the acute rewarding effects of drugs cannot account for several major features of addiction, including relapse to drug use following prolonged abstinence [8-10] and the transition from controlled drug intake to excessive and compulsive drug use [11-14].

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Based on several lines of evidence, it has been hypothesized that compulsive drug-seeking and drug relapse is mediated in part by drug-induced changes in the orbitofrontal cortex (OFC) [14-18]. Hypermetabolic activity in OFC has been implicated in the etiology of obsessive compulsive disorders (OCD) [19-22], and there is evidence that the incidence of OCD in drug abusers is higher than the rate in the general population [23-25]. Imaging studies in cocaine [26; 27], methamphetamine [28; 29] and heroin [15] users reveal altered metabolism in the OFC and increased neuronal activation in response to drug-associated cues [15; 30]. Although it is difficult to know whether metabolic changes reflect enhanced or disrupted neural function, altered neuronal signaling in both OCD patients and drug addicts likely reflects abnormal integration of input from afferent areas. Consistent with this speculation, drug addicts, like patients with OFC damage [31], fail to respond appropriately in several variants of the 'gambling' task [32-34]. This poor performance is accompanied by abnormal activation of OFC [35]. The results from these clinical studies indicate that OFC function is impaired in drug addict, but importantly these data cannot distinguish whether changes in OFC function are induced by drug exposure or represent a pre-existing condition that predispose individuals to drug addiction. This issue can be addressed in studies using animal models.

In this review, we first discuss the putative function of the OFC in guiding behavior. We then discuss evidence from laboratory studies on the effect of drug exposure on OFC-mediated behaviors and on neuronal structure and activity in OFC. We then discuss the limited literature on the role of the OFC in drug self-administration and drug relapse in animal models. We conclude that while there is clear evidence that drug exposure causes long-lasting changes in neuronal structure and activity in OFC and impairs OFC-dependent behaviors, the precise role these changes play in compulsive drug use and relapse has not yet been established. Table 1 provides a glossary of terms used in our review (*italic letters* in the text).

Role of OFC in guiding behavior

Broadly speaking, behavior can be mediated by a desire to obtain a particular outcome, which involves active representation of the value of that outcome, or by habits, which dictate a particular response in a particular circumstance regardless of the value or desirability (or undesirability) of the outcome. Ample evidence now demonstrates that a circuit including the OFC is particularly critical for promoting behavior based on active representation of the value of the expected outcome [36]. This function is evident in the ability of animals to rapidly adjust responses when predicted outcomes change [37-39]. In rats and monkeys, this ability is often assessed in *reversal learning* tasks in which a cue predictive of reward becomes predictive of non-reward (or punishment) and a cue predictive of non-reward (or punishment) becomes predictive of reward. Imaging studies implicate OFC in reversal learning in humans [40-42], and rats and primates with damage to the OFC are impaired at learning reversals even when learning for the original materials is intact [38; 43-51]. This deficit is illustrated in rats in Figure 1A. OFC lesions may disrupt a similar function in 'gambling' tasks in which intact subjects learn to change their responding for a cue that initially predicts a high value, but later comes to predict a high risk of losses [31]. Although it is currently a controversial topic in cognitive neuroscience, there is evidence that the role of the OFC in the gambling task is largely accounted for by the requirement for reversal learning that is inherent in the design of most gambling tasks [51].

The involvement of OFC in representing the value of predicted outcomes can be isolated in *reinforcer devaluation* tasks, in which the value of the outcome is directly manipulated via pairing with illness or selective satiation [52]. In these settings, normal animals will respond less for predictive cues after devaluation of the predicted outcome. Rats and non-human primates with damage to the OFC fail to show this effect of outcome devaluation [37; 38; 53]. These studies reveal a specific deficit in the ability of OFC-lesioned animals to utilize a representation of the outcome's current value to guide their behavior, particularly in response to conditioned

cues. As a result, behavior evoked by the cues becomes less based on the value of the expected outcome and, by default, more habit-like. Though these studies have been done in laboratory animals, imaging studies have shown that cue-evoked BOLD responses in OFC are highly sensitive to devaluation of the foods they predict [54]. Below, we discuss evidence that repeated drug exposure induces alterations in neuronal and molecular markers of function in OFC; these changes likely mediate the observed impairments in OFC-mediated behaviors in drug-experienced laboratory animals. Such changes might also lead, in part, to the habit-like response patterns evident in the behavior of addicts and drug-experienced animals.

Effect of drug exposure on OFC

It remains an open question what brain areas and changes mediate the inability of addicts to control their behavior. One way to address this question is to examine whether normal behaviors, which depend on particular brain regions or circuits, are affected by drug exposure, and to relate changes in normal learning with drug-seeking behavior in a relevant animal model. If the loss of control over drug seeking reflects drug-induced changes in particular brain circuits, then the impact of these changes should be evident in behaviors that depend on those circuits. In this regard, drug exposure has been shown to affect several learned behaviors mediated by prefrontal regions, amygdala, and striatum in rats [55-58]. Drug exposure also alters how neurons process learned information in these brain areas [59; 60]. Among these studies, there is now evidence that cocaine exposure disrupts outcome-guided behavior that depends on the OFC. For example, rats previously exposed to cocaine for 14 days (30 mg/kg/day, i.p.) failed to modify conditioned responding after reinforcer devaluation approximately 1 month after withdrawal [57]. Cocaine-experienced rats also respond impulsively when reward size and time to reward is manipulated in choice tasks several months after withdrawal [61; 62]. These deficits are similar to those caused by OFC lesions [37; 63].

Reversal learning is also impaired after cocaine exposure. This was first shown by Jentsch and Taylor [64] in monkeys given chronic intermittent exposure to cocaine for 14 days (2 or 4 mg/kg/day, i.p.). These monkeys were slower to acquire reversals of object discriminations when tested 9 and 30 days after withdrawal from cocaine. Similarly, we have found that rats previously exposed to cocaine (30 mg/kg/day i.p. for 14 days) exhibit impaired reversal performance approximately 1 month after withdrawal from the drug [65]. As illustrated in Figure 1B, this deficit in reversal learning is of similar magnitude to that of rats with OFC lesions [50; 65; 66].

This reversal learning deficit is associated with a failure of OFC neurons to signal the expected outcomes appropriately [59]. Neurons were recorded from the OFC in a task similar to the one used above to demonstrate reversal-learning impairments; each day the rats learned a novel go, no-go odor discrimination, in which they responded to odor cues to obtain sucrose and to avoid quinine. The OFC neurons, recorded in rats exposed to cocaine over a month earlier, fired normally to the sucrose and quinine outcomes, but failed to develop cue-selective responses after learning. In other words, neurons in the cocaine-treated rats did not signal the outcomes during odor sampling, when that information could be used to guide the response. The loss of this signal was particularly apparent during sampling of the cue that predicted the aversive quinine outcome and was associated with abnormal changes in response latencies on these aversive trials. Furthermore, upon reversal of the cue-outcome associations, the OFC neurons in cocaine-treated rats with enduring reversal impairments failed to reverse their cue-selectivity. These results are consistent with the hypothesis that cocaine-induced neuroadaptations disrupt the normal outcome signaling function of the OFC, thereby altering the ability of the animal to engage adaptive decision-making processes that depend on this function [14; 67]. These results also suggest that abnormal OFC function observed in addicts likely reflects drug-induced changes rather than or in addition to pre-existing OFC dysfunction.

Of course, there are substantial perils in using the results of lesion studies to infer what areas are affected by drug exposure. The effects of drug exposure are clearly not equivalent to a lesion, and distal effects in other structures could well mimic the effects of lesions. Yet work in laboratory animals demonstrates that psychostimulant exposure does cause changes in markers of function in the OFC. For example, rats trained to self-administer amphetamine exhibit long-lasting decreases in OFC dendritic density [68]. In addition, amphetamine-experienced rats exhibit less plasticity in their dendritic fields in the OFC after instrumental training when compared to controls [68]. Notably, these results stand in contrast to findings in most other brain areas that have been studied, including other parts of prefrontal cortex, where psychostimulant exposure typically increases dendritic spine density, likely reflecting increased neuronal plasticity [69-71]. These results specify the OFC as an area that exhibits a lasting decline in plasticity – or the ability to encode new information – as a result of exposure to psychostimulants. Consistent with this, cocaine addicts show decreased gray matter concentration in the OFC [72].

There are several issues to consider regarding the relevance of the results of the behavioral studies reviewed above to the human condition. One issue is that in all of the studies reviewed above, drugs were given non-contingently, using exposure regimens that lead to enduring *psychomotor sensitization* [73; 74]. Several studies have shown important differences in the effects of contingent and non-contingent drug exposure on brain function and behavior [75-78]. In addition, there is little evidence that psychomotor sensitization is manifested in either chronic cocaine addicts or in monkeys with extensive history of cocaine self-administration [79]. Thus, it is important to establish that deficits in OFC-dependent functions observed following non-contingent cocaine exposure regimens are also observed in drug addiction models that incorporate contingent drug use (i.e., drug self-administration). Accordingly, we have recently reported that rats trained to self-administer cocaine for 14 d for 3 h/d (0.75 mg/kg/infusion) demonstrated a profound reversal learning deficit up to three months after withdrawal from the drug [80]. As illustrated in Figure 1C, this reversal deficit was similar in magnitude to that observed after non-contingent cocaine exposure [65] or after OFC lesions [50].

Another issue to consider is that in all of these studies, OFC deficits were demonstrated in laboratory animals that were abstinent for some period of time. As a result, the time course and duration of the effect of drug-exposure on OFC function is largely unknown. One exception is a study by Kantak and colleagues [81] in which they tested the effect of ongoing cocaine exposure on an OFC-dependent odor-guided win-shift task [82]. These authors reported that behavior in this task was impaired by contingent but not non-contingent cocaine in rats that were tested immediately after ongoing cocaine self-administration sessions. This result shows that cocaine exposure can have an immediate effect on OFC-dependent functions. Interestingly, the failure of non-contingent cocaine exposure on OFC-mediated behaviors in this study compared to the reports reviewed above suggests that the impact of drug-exposure on OFC function may increase after withdrawal from the drug.

In conclusion, cocaine exposure (either contingent or non-contingent) leads to long-lasting deficits in OFC-dependent behaviors that are similar in magnitude to those observed after OFC lesions. Non-contingent cocaine exposure also leads to structural changes in OFC neurons, likely reflecting decreased plasticity in these neurons, as well as abnormal neuronal encoding in the OFC. Next, we describe results from studies that have examined the role of OFC in drug reward and relapse, as measured in the drug self-administration [83] and reinstatement [84] models.

Role of OFC in drug self-administration and relapse

The data reviewed above indicate that OFC function is altered by repeated drug exposure. A question derived from these data is what role the OFC plays in mediating drug-taking behavior in animal models. Surprisingly few papers have assessed this question directly. In an early study, Phillips et al. [85] reported that four rhesus monkeys reliably self-administered amphetamine (10^{-6} M) into the OFC. Surprisingly, the same monkeys did not self-administer amphetamine into the nucleus accumbens, an area known to be involved in the rewarding effects of amphetamine in rats [86]. Hutcheson and Everitt [87] and Fuchs et al. [88] reported that neurotoxic OFC lesions did not impair the acquisition of cocaine self-administration under a fixed-ratio-1 reinforcement schedule in rats. Hutcheson and Everitt [87] also reported that OFC lesions had no effect on the dose-response curve for self-administered cocaine (0.01 to 1.5 mg/kg). Although it is difficult to compare the rat and monkey studies because of differences in drug used and routes of administration, and potential species differences in OFC anatomy [89], the results of the rat studies suggest that the OFC is not critical for the rewarding effects of self-administered intravenous cocaine. This observation is similar to results in normal learning studies, which show that OFC lesions typically have no effect on learning to respond for non-drug rewards in a variety of settings [37; 50; 90].

By contrast, Hutcheson and Everitt [87] found that the OFC was required for the *conditioned reinforcing* effects of cocaine-associated cues, as measured in a *second-order schedule of reinforcement procedure* [91; 92]. They reported that neurotoxic OFC lesions impaired the ability of the cocaine Pavlovian cues to maintain instrumental responding. Similarly, Fuchs et al. [88] reported that reversible inactivation of the lateral (but not medial) OFC with a mixture of a GABAa+GABAb agonists (muscimol+baclofen) impaired the conditioned reinforcing effects of cocaine cues, as measured in *a discrete cue-induced reinstatement procedure*. Additional potential evidence for OFC's role in cue-induced cocaine seeking is that exposure to cues previously paired with cocaine self-administration increases the expression of the immediately early gene *Zif268* (a marker of neuronal activation) in this region [93]. Together these data indicate that the OFC plays an important role in mediating the specific ability of drug-associated cues to motivate drug-seeking behavior. Such a role may reflect the OFC's previously described role in the acquisition and use of cue-outcome associations [37; 38; 53]. Indeed, OFC lesions impair responding for conditioned reinforcement in non-drug settings [94-96] and have also been recently reported to affect *Pavlovian-to-instrumental transfer* [90], indicating that the OFC supports the ability of Pavlovian cues to guide instrumental responding.

Interestingly, Fuchs et al. [88] reported a different pattern of results when they made lesions of the lateral or medial OFC prior to training. They found that these pre-training lesions had no effect on cue-induced reinstatement of cocaine seeking. Because these lesions were made prior to self-administration training, the OFC was not available to participate in acquisition of the cue-cocaine associations. As a result, the lesioned rats may have learned to rely more on other brain areas that are involved in cue-induced cocaine seeking [97].

Finally, the OFC also appears to be important for stress-induced reinstatement of drug-seeking. Previous studies using a reinstatement procedure [10; 98] have shown that exposure to intermittent footshock stress reinstates drug seeking after training for drug self-administration and subsequent extinction of the drug-reinforced responding [99; 100]. Recently, Capriles et al. [101] compared the role of the OFC in stress-induced reinstatement and reinstatement induced by cocaine priming injections. They found that reversible inactivation of the OFC with tetrodotoxin decreased footshock stress- but not cocaine-induced reinstatement of cocaine seeking. They also reported that injections of the D1-like receptor antagonist SCH 23390 but not the D2-like receptor antagonist raclopride into the OFC blocked stress-induced reinstatement.

In conclusion, the limited literature reviewed above suggest that the OFC likely does not mediate the acute rewarding effects of self-administered cocaine, but is involved in the ability of cocaine cues and stressors to promote drug seeking. In addition, D1-like dopamine receptors in the OFC are involved in stress-induced relapse to cocaine seeking.

Conclusions and future directions

The results of studies using self-administration and reinstatement procedures suggest a complex role of the OFC in drug reward and relapse. We would draw several tentative conclusions from these pre-clinical studies. First, the OFC does not appear to play an important role in the acute rewarding effect of cocaine or in relapse induced by acute exposure to the drug. This result is consistent with data showing that the OFC is rarely necessary for animals to learn to respond for reward, presumably due to the operation of multiple, parallel learning systems [37; 50; 90].

Second, the OFC does appear to play an important role in the ability of drug-associated cues to provoke cocaine seeking. These findings are in agreement with results from imaging studies demonstrating strong activation of the OFC by drug-associated cues [15]. Lesions or reversible inactivation of the OFC may decrease cue-induced drug seeking, because of a failure to normally activate information regarding the expected value of the drug [36]. One question for future research is the time-course of drug-induced changes in OFC and whether the OFC is involved in the time-dependent increases in cue-induced cocaine seeking after withdrawal [102-104], a phenomenon termed *incubation of craving*.

Third, the OFC also appears to be important for stress-induced reinstatement of cocaine seeking. It has been reported that the effect of footshock stress on reinstatement of cocaine seeking is dependent on the presence of a discrete tone-light cue [105]. Thus, the role of the OFC in mediating stress-induced reinstatement may be secondary to the effect of the stress manipulations on cue-controlled responding.

It is important to emphasize that our conclusions regarding the role of the OFC in drug self-administration and relapse are somewhat speculative given the very limited data. One issue to consider is that the contribution of the OFC to drug-seeking behaviors may reflect changes in the OFC caused by previous exposure to the drug. Because of this consideration, interpreting the effects of lesions or other pharmacological manipulations of the OFC on drug-seeking induced by cues or stress in rats with a history of drug self-administration must be done with caution.

A second and perhaps more fundamental issue to consider is that the current animal models of drug self-administration and relapse may not be suitable for assessing what role the OFC plays in human drug addiction. In addition to its general role in mediating outcome-guided behaviors, the OFC seems to be particularly important for recognizing and responding to changes in expected outcomes [38; 43; 50]. This is particularly evident when outcomes change from good to bad or when they become delayed or probabilistic [37; 50; 63; 106-108]. Here we have reviewed evidence that this particular function of the OFC is disrupted by exposure to addictive drugs, leading to maladaptive and impulsive decision-making [57; 58; 61; 62; 64; 65; 80]. Given that drug-seeking behavior in humans is likely the consequence of the balance between the momentary desire for the drug and the evaluation of the typically probabilistic and often delayed consequences of drug seeking [109-111], effects of drugs on the ability of the OFC to correctly signal delayed or probabilistic outcomes might underlie the inability of addicts to forgo the short-term and immediate gratification of drug use. Yet such effects would not be evident in most current models of drug use and relapse, which typically do not model the addict's conflict between immediate and delayed outcomes.

Although earlier studies did incorporate punishment procedures for assessing the drug reinforcement [112; 113], only recently have several addiction researchers returned to these models. These researchers have reported that some rats with an extensive history of exposure to drugs will continue to engage in drug-taking behavior when confronted with punishment or adverse consequences that normally would suppress drug- or food-taking responding [114-116]. Punishment- or conflict-based procedures were also recently introduced to assess drug-priming- and cue-induced relapse to drug seeking [117]. These procedures may be better suited to isolate the role of the OFC in drug addiction, because they more closely model the known roles of the OFC in behavior as well as behavior of the human drug addict. Thus, assessing the role of the OFC in punishment or conflict models is an important area of future research. In this regard, based on the findings on the reversal learning deficits after cocaine exposure, we predict that cocaine-induced alterations in OFC functioning will be associated with a diminished ability to suppress responding in the presence of adverse consequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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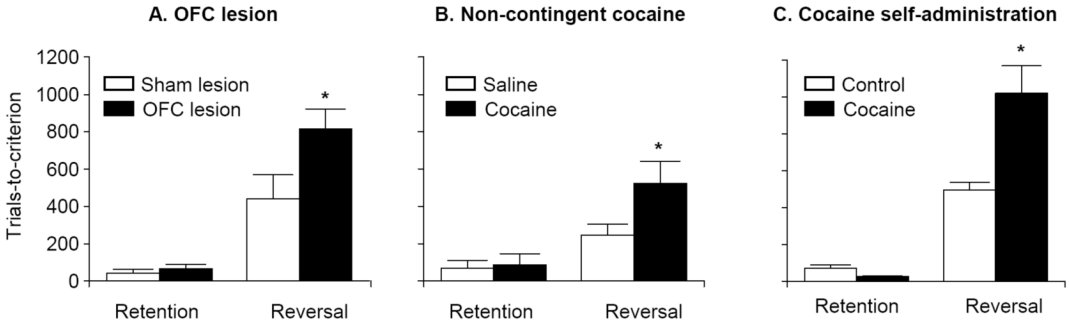

Figure 1. Cocaine exposure induces OFC-dependent reversal learning deficits that are of similar magnitude to learning deficits induced by OFC lesions

(A) Effect of OFC lesions on reversal learning. Sham and OFC-lesioned rats were tested on serial reversals of a post-operatively acquired 2-odor go, no-go discrimination. One odor predicted sucrose availability, while a second odor predicted quinine. Rats had to learn to respond for sucrose but withhold responding for quinine; criterion was 90% correct responding in a block of 20 trials. OFC lesions had no effect on retention but impaired reversal learning. **(B)** Effect of repeated non-contingent cocaine exposure (30 mg/kg/day X 14 days) on reversal learning. Rats were injected with cocaine or saline and were then tested on the same odor discrimination reversal task used in (A) after approximately 1 month of withdrawal from the drug. Cocaine exposure had no effect on retention but impaired reversal learning. **(C)** Effect of contingent cocaine self-administration (0.75 mg/kg/infusion, 4 h/day X 14 days) on reversal learning. Rats were trained to self-administer cocaine and then tested on the same odor discrimination reversal task used in (A) after approximately 3 months of withdrawal from the drug. Cocaine self-administration had no effect on retention but impaired reversal learning. * Different from the respective controls, $p < 0.05$. Data in (A), (B), and (C) were adapted from references 49, 64 and 80, respectively.