

The Orbitofrontal Cortex, Impulsivity, and Addiction

Probing Orbitofrontal Dysfunction at the Neural, Neurochemical, and Molecular Level

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ABSTRACT: The association between impulsivity and addiction is currently a topic of intense research interest. Investigations into the neurobiological basis of aspects of impulse control have revealed some striking parallels between the brain circuitry and neurochemical systems implicated in drug dependence and impulsive behavior. Both processes are heavily regulated by limbic corticostriatal circuits including the orbitofrontal cortex (OFC) and nucleus accumbens (NAC), and are modulated by dopamine (DA) and serotonin (5-HT). Hypoactivity within the OFC has been observed in recently abstinent cocaine users, and this is thought to contribute to the cognitive deficits associated with drug abuse, including impairments in impulse control. However, the neurobiological mechanisms underlying these functional and behavioral deficits are unclear. In parallel to observations made in the NAC, recent data indicate that chronic cocaine use also induces the transcription factor Δ FosB in the OFC and that this plays a role in the cognitive sequelae of chronic cocaine administration. In particular, Δ FosB appears to be involved in the development of tolerance to the disruptive effects of acute cocaine on impulsivity and motivation observed after repeated cocaine administration. Increased Δ FosB also contributes to increased impulsivity during withdrawal from the drug. Both effects could be attributed to the up-regulation of local inhibitory processes in the OFC after over-expression of Δ FosB and chronic cocaine treatment. Through integrating what is known of the interaction between addictive drugs and impulsivity at the neural, neurochemical, and molecular level, novel insight may be obtained into the multi-faceted regulation of the addicted state.

KEYWORDS: cocaine; five-choice serial reaction time task; delay-discounting; Δ FosB; dopamine; serotonin

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INTRODUCTION

Broadly defined as action without sufficient foresight, high levels of impulsivity are associated with a range of psychiatric disorders, most notably bipolar depression and attention-deficit hyperactivity disorder (ADHD). However, contemporary studies have identified deficits in impulse control as a contributing factor to drug addiction. Although research to date has largely focused on understanding the reinforcing effects of addictive drugs,¹ recent evidence indicates that cognitive changes caused by cocaine and other drugs of abuse are also important in the generation and maintenance of addiction and may determine whether therapy is successful.^{2,3} Research into the biological basis of impulse control indicates that some of the same brain structures and neurotransmitter systems are implicated in both addiction and impulsivity. In particular, the orbitofrontal cortex (OFC) and nucleus accumbens (NAC) have been identified as important loci of impulse control. In terms of its role in addiction, it has been firmly established that drug-induced changes in dopamine (DA) within the NAC signal the rewarding properties of addictive drugs and the stimuli associated with them.⁴ However, the role played by the OFC in the development of addiction and how hypoactivity in this region may relate to the maladaptive decision making and impulsive behavior seen in substance abusers, have not been sufficiently clarified. Following a brief discussion of the definition and measurement of impulsivity, the relationship between impulsivity and addiction will be reviewed with a focus on the OFC. Current information regarding the extent to which manipulations of the OFC at the neural, neurochemical, and molecular level alter impulsivity and addiction will be presented and future directions for research outlined.

DEFINING IMPULSIVITY

Understanding exactly what we mean by the term “impulsivity” has proven more problematic than superficial discussion would suggest. Clinical psychologists have designed self-report questionnaires to measure impulsive behavior, such as the Barratt Impulsiveness scale⁵ and the I7.⁶ Factor analysis of data from such questionnaires largely suggests that impulsive behavior consists of several independent dimensions, although there is considerable variation as to the precise definition of these constituent parts (see Ref. 7 for review). However, common themes include decreased inhibitory control (or behavioral disinhibition), intolerance of delay to rewards, and quick decision making due to lack of consideration. Aspects of impulsivity are also thought to relate to poor attentional ability and hyperactivity. Bearing in mind this diversity of processes, one definition of impulsivity which still seems particularly appropriate is that “impulsivity encompasses a range of actions which are poorly

conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences” (p. 23).⁸

Given the apparent multifaceted nature of the phenomena collectively described as impulsive, it has been suggested that impulsivity is not a unitary construct, but rather incorporates multiple distinct psychological processes, which may have independent underlying biological mechanisms.^{7,9} This has led some to question the utility of the concept of impulsivity in and of itself. However, in exploring the neural bases of aspects of impulsivity, it becomes clear that similar, interconnecting networks of neural structures are employed in regulating different forms of impulse control, although the relative importance of different structures or neurotransmitter systems may vary with the exact process under examination.¹⁰ Furthermore, the combined use of two independent measures of impulsivity is able to accurately diagnose ADHD far more effectively than the use of either measure in isolation, suggesting that the impulsivity construct is still of significant clinical import despite its apparent complexity.¹¹

Measuring Impulsivity

Through focusing on different aspects of impulsive behavior, it has proved possible to devise a variety of behavioral paradigms to measure impulsivity in both human and non-human subjects. These can be broadly divided into two categories: those measuring impulsive choice or impulsive decision making and those measuring impulsive action or motoric impulsivity.

Impulsive action can be broadly defined as the inability to withhold from making a response. One of the most ubiquitous and well-characterized tasks designed for rats is the five-choice serial reaction time task (5CSRT).¹² This task was developed as a test of sustained and divided attention for rodents based on the continuous performance task (CPT) used to monitor attentional function in humans.¹³ During the 5CSRT, the animal is required to make a nosepoke response in one of five apertures upon brief illumination of a stimulus light located therein. Subsequent to beginning a trial and prior to illumination of a stimulus light, there is a 5 s inter-trial interval during which the animal must withhold from responding at the five-hole array. Any responses made during this time are described as premature responses, and are punished. These premature responses provide an index of motoric impulsivity and are potentially analogous to “false alarm” errors made in the CPT.

In order to model impulsive decision making, an alternative task must be used. One of the most widely used measurements of impulsive decision making in laboratory animals is the delay-discounting or delay-to-gratification model of impulsive choice. Here, the subject chooses between a small reward delivered immediately and a larger reward delivered after a delay. Although the concept appears simple, many variants of the task have been developed.

One of the most prevalent is that first published by Evenden and Ryan in which animals choose to respond on two levers, one of which provides a small reward of one pellet, the other a large reward of four pellets.¹⁴ Each session is divided into blocks of 12 trials, the first two of which are forced choice. In each successive block, the delay to the large reward increases from 0 s in the first block, to 10, 20, 40, and finally 60 s in the last block. In order to ensure that choice of the large reward option would always maximize the amount of reward earned, the length of each trial is kept constant so that the animal cannot accrue more pellets or increase the rate of reinforcement by repeatedly choosing the small reward. Using this paradigm, a within-session delay-discounting curve can be obtained. Animals typically show a strong preference for the larger reward early in the session when the delay to its delivery is short or absent, but shift their preference to the smaller reward as delay to the larger reward increases. This shift indicates an increase in impulsive choice. There is no measure of motoric impulsivity in this paradigm.

Together, these behavioral paradigms have been used in numerous studies to probe the neural and neurochemical mechanisms that regulate impulsivity. For example, manipulations of the NAC and medial prefrontal cortex (mPFC) have been found to affect performance of these tasks, e.g.^{15,16} However, the same brain regions are not always involved in all measures of impulse control, and damage to the same region can sometimes have discordant and even opposing effects on impulse control depending on how impulsivity is defined. For example, lesions to the anterior cingulate cortex have been shown to increase premature responding on the 5CSRT,¹⁶ but lesions to this region do not alter impulsive choice.¹⁵ Damage to the NAC increases impulsive choice dramatically,¹⁵ but the effects on 5CSRT performance are subtle.¹⁷ More specifically, when the data are averaged over the whole session, there is no clear effect of NAC lesions on the level of premature responding. However, on closer analysis, it becomes apparent that NAC-lesioned rats were generally more likely to make a premature response after they had made an incorrect choice, an effect which was also observed after disconnection lesions of the NAC and mPFC. Such effects highlight the importance of frontostriatal circuitry in integrating information about task contingencies and response selection, and may also relate to the putative relationship between the assessment of negative feedback and the propensity to be impulsive.¹⁸

It would therefore appear that, although common regions within the affective frontostriatal loop are implicated in multiple forms of impulse control, the precise role that an individual area plays in a specific aspect of impulsivity varies according to the task demands and likely reflects the roles these regions play in other aspects of goal-directed behavior. Furthermore, the behavioral effects of modulating neurotransmitter levels in these different regions may also be an important consideration (see Ref. 10 for further discussion). In light of these observations, the following paragraphs will focus on data pertaining to the OFC.

COMMON NEURAL CIRCUITRY IN IMPULSIVITY AND ADDICTION: FOCUS ON THE OFC

In humans, damage to the OFC results in a pattern of maladaptive decision making and aberrant social behavior that is often described as impulsive, despite relatively normal IQ, language ability, and general measurements of cognitive ability. The impairment noted in OFC patients is often exemplified by their poor performance on laboratory-based gambling tasks, such as that devised by Bechara, Damasio, and colleagues (the Iowa gambling task).¹⁹ On each trial, subjects choose cards from four decks to accumulate points. The optimal strategy is to choose cards from the two decks associated with small immediate gains but also low and infrequent losses, an approach which healthy volunteers learn during the course of the session. Persistent selection from the two disadvantageous decks leads to large immediate gain but heavy losses in the long term. This pattern of risky decision making is observed in pathological gamblers,²⁰ substance abusers,²¹ and patients with damage to the OFC or basolateral amygdala.²²

Imaging studies have revealed that the OFC is hypoactive in recently abstinent cocaine abusers,^{23–25} and it has been suggested that this reduced cortical activity may contribute to the elevated levels of impulsivity seen in addicts. In addition to their poor performance on gambling tasks, people with a history of drug addiction make more premature-like responses on a version of the CPT known as the immediate and delayed memory task.²⁶ Data from such behavioral experiments complement results obtained from self-report questionnaires, such as those measuring delay-discounting performance, which indicate that addicts are less tolerant to delay of reward.^{27,28} Collectively, these data suggest that addicts show deficits in a variety of different types of impulse control.

In terms of animal models of addiction and impulsivity, lesions to the OFC increase premature and perseverative responding on the 5CSRT. Furthermore, animals that were innately more impulsive on the 5CSRT also self-administered significantly more cocaine.²⁹ PET scans of more impulsive animals that were drug naive also revealed decreases in DA D₂ receptor binding within the NAC. Interestingly, a similar pattern of data has been observed in human drug addicts.³⁰ These data suggest that changes in dopaminergic function within the NAC may be a trait marker for impulsivity, which impacts upon the development of addiction. Whether these animals also show alterations in OFC function is yet to be established. However, using the delay-discounting paradigm developed by Evenden and Ryan, damage to the OFC has been reported to increase choice of the larger, delayed reward,³¹ i.e., decrease impulsive choice. Although seemingly paradoxical, this persistent choice of the large reward despite its associated aversive consequences (i.e., the delay) could reflect a “myopia for the future” comparable to that reported on laboratory-based gambling tasks in human patients with OFC damage.¹⁹ As

such, damage to the OFC may prevent the adequate integration of information about the consequences of responding for a reward with the subjective value of that rewarding outcome,³² such that delay fails to sufficiently devalue the larger reward.

In summary, there appears to be considerable overlap between the effects of damage or reduced activity within the OFC and the effects of long-term exposure to addictive drugs on measures of impulse control. Although other brain regions such as the NAC are almost certainly involved in the generation of the addicted state, drug-induced changes within the OFC may also be important in mediating the cognitive sequelae of addiction.

NEUROCHEMICAL REGULATION OF IMPULSIVITY: FOCUS ON THE OFC

Amphetamine and cocaine acutely increase measures of impulsive action in rats.^{33,34} However, stimulant drugs are also used to treat the increased impulsivity evident in ADHD, an apparent paradox that may reflect the fact that the effects of dopaminergic drugs may depend on the basal level of dopaminergic activity.³⁵ In parallel to the effects of OFC lesions, psychostimulants have also been shown to increase choice of the larger, delayed reward in delay-discounting paradigms.³⁶⁻⁴⁰ It would therefore appear that cocaine and amphetamine acutely increase behavioral disinhibition and promote the selection of larger rewards regardless of the aversive consequences. Such a pattern of behavior is strikingly similar to the effects of OFC lesions and has been interpreted as reflecting an increase in incentive motivation for reward.⁴¹ The ability of addictive drugs to hijack the reward system has been largely attributed to their enhancement of dopaminergic activity, and it is clear that the dopaminergic system also has an important role to play in the regulation of impulsivity. The ability of amphetamine to increase premature responding on the 5CSRT can be blocked by lesions to the dopaminergic terminals within the NAC and can be attenuated by systemic administration of the DA D₂ receptor antagonist eticlopride.^{34,42} However, global reductions in serotonin (5-HT) levels also impair the ability of amphetamine to increase impulsivity on the 5CSRT,⁴³ and levels of 5-HT rather than DA within the mPFC correlate with the number of premature responses made by individual animals.⁴⁴ Thus, although both 5-HT and DA are implicated in the regulation of this form of impulsivity, there may be some redundancy within these signaling pathways. The effects of dopaminergic or serotonergic manipulations targeting the OFC on 5CSRT performance have yet to be determined.

In parallel to impulsive action, the ability of amphetamine to modulate delay-discounting performance can also be affected by both dopaminergic and serotonergic manipulations,^{37,39} although the dopaminergic input to the NAC appears less important for amphetamine's effects in this paradigm.⁴⁰ However,

selective lesions to the dopaminergic terminals within the OFC produced effects similar to the amphetamine and OFC lesions in that choice of the larger but delayed reward was increased.⁴⁵ It would therefore seem that too much or too little DA in the OFC may limit the ability of this region to update the representation of the value of a reward when that value changes, i.e. to decrease the subjective value of the larger reward as it becomes increasingly delayed.

Exactly what DA is signaling within the OFC therefore remains an intriguing question. Data using *in vivo* microdialysis reveal that increases in dopaminergic activity are observed when animals are engaged in performing delay-discounting judgments, but not in animals that were yoked to those making the choice between the large and small rewards.⁴⁶ Levels of the dopaminergic metabolite DOPAC were also higher at the beginning of the session, when delay to the large reward was short, compared to the end of the session, when delay to the large reward was longer. These findings suggest that DA in this region does more than signal the occurrence or expectation of reward delivery, and it is tempting to speculate that dopaminergic innervation to the OFC is indeed involved in signaling the changing value of the larger reward as it becomes progressively more delayed. However, further work is needed to determine the validity of this hypothesis. Likewise, whether DA in this region is also involved in mediating 5CSRT performance remains to be investigated either through *in vivo* microdialysis or direct drug infusions. Given the parallels between psychostimulant medication and OFC damage observed in the delay-discounting paradigm, it is possible to speculate that too much or too little DA in the OFC would likewise increase premature responding.

EXPLORING THE COGNITIVE SEQUELAE OF ADDICTIVE DRUGS ON TEST OF IMPULSIVITY

While it is clear that drugs which act on the dopaminergic and serotonergic systems can acutely alter impulsive responding, less is known about the effects of repeated administration of drugs of abuse, and how such administration may affect the cognitive response to a subsequent drug challenge. Exploring these issues may provide insight into the cognitive changes which accompany the development of addiction, as well as the neurobiological mechanisms which lead to under-activity of the OFC in cocaine addicts.

Acute administration of cocaine (0–20 mg/kg intraperitoneally [IP]) produces a range of cognitive impairments on the 5CSRT, increasing premature responding and the number of omissions, as well as decreasing the accuracy of target detection and the number of trials completed at higher doses.^{34,47} In comparison to the effects of amphetamine, cocaine also increases choice of the larger delayed reward in the delay-discounting paradigm (0–15 mg/kg IP).⁴⁷ However, if animals are treated chronically with cocaine (2 × 15 mg/kg

IP for 21 days) and then challenged again with an acute injection of cocaine on-task, many of these cognitive changes are no longer evident.⁴⁷ A similar reduction in the ability of amphetamine to increase premature responding in animals with a history of cocaine self-administration has also been reported.⁴⁸ Surprisingly, it would therefore appear that repeated exposure to an addictive substance produces tolerance to its disruptive effects on motivation and impulsivity. These effects are particularly unexpected given that chronic exposure to cocaine increases the hyperactivity caused by an acute injection of the drug, a phenomenon known as locomotor sensitization.

However, tolerance to the effects of addictive drugs is hardly a new concept in the addiction literature. The rewarding or euphoric effects of cocaine certainly diminish with repeated use, and one of the major criticisms of the use of locomotor sensitization to model addiction is that sensitization to the arousing effects of cocaine are not reported clinically.⁴⁹ Furthermore, tolerance to the effects of cocaine may be one factor which contributes to escalating drug use and increased drug dependency.⁵⁰ Hence, repeated drug use leads to compensatory processes in the brain which combat the drugs' enjoyable effects, and these compensatory processes may lead to increased drug intake. In parallel, compensatory processes may limit the impact on cognition of an acute dose of cocaine, but could also have disadvantageous consequences. For example, given that cocaine is a stimulant drug and increases excitatory activity in the OFC, it is probable that any compensatory process designed to reduce the impact of cocaine on OFC function would be inhibitory in nature. Upregulating inhibitory processes in the OFC is unlikely to be without consequences (see previous discussion) and may lay the groundwork for cognitive deficits during withdrawal. The following theoretical framework therefore emerges: during chronic cocaine use, stimulation of the OFC is higher than normal and inhibitory processes are engaged to reduce OFC activation level to the optimal status quo. However, if cocaine intake ceases, as in withdrawal, drug-induced stimulation of the OFC stops. The compensatory inhibitory processes which developed to preserve OFC function now act to reduce OFC activation below the level of optimal functioning, and cognitive impairment may result.

Consistent with this hypothesis are the findings from imaging studies indicating that the OFC is under-active in recently abstinent cocaine addicts (see above) and that this under-activity can be reversed by administration of the cocaine analogue procaine.⁵¹ If the cortex really does adapt to drug-induced stimulation such that the threshold for activation is higher, and if this does contribute to cognitive dysfunction during withdrawal, then controlled administration of the abused drug or a pharmacological analogue may be beneficial in the treatment of addiction. Certainly maintenance therapy of this kind is available for opiate dependence,⁵² but its efficacy is thought to stem from reduced craving or a decrease in the pleasant sensations induced by the abused drug; the effects of maintenance therapy on cognitive function has not been determined. Interestingly, the stimulant drug modafinil has recently been used in

clinical trials to reduce cocaine dependence and relapse.⁵³ Whether modafinil improves cognitive dysfunction in abstinent cocaine users has not been determined, though it has been shown to have pro-cognitive effects in and of itself.⁵⁴

Another question concerns the mechanism underlying the induction of these putative compensatory changes. In addition to their effects on monoaminergic neurotransmitter systems, the impact of addictive drugs on brain function can also be determined at the level of intracellular signaling pathways and gene transcription. Some observations made within this domain may reveal how repeated exposure to addictive drugs causes such long-term changes in brain function and behavior⁵⁵⁻⁵⁷ and may provide insight into drug-induced dysfunction within the OFC.

MOLECULAR CHANGES ASSOCIATED WITH ADDICTION WITHIN THE OFC: ROLE IN IMPULSIVITY

One line of investigation has focused on transcription factors, nuclear proteins which bind to the regulatory regions of certain genes and change the rate at which they are transcribed. It has been observed that a truncated splice variant of FosB known as Δ FosB is only expressed at high levels after chronic rather than acute administration of a variety of abused substances, including cocaine, morphine, and nicotine.⁵⁸ Once expressed, it is relatively stable and can persist in the brain for weeks after the last drug exposure. Furthermore, downstream targets of Δ FosB include proteins involved in synaptic plasticity, such as cyclin-dependent kinase 5, induction of which could lead to relatively permanent changes in neuronal connectivity.⁵⁹ As such, induction of Δ FosB may contribute to the regulation of gene transcription in a manner relevant to the development of addiction. The majority of work undertaken to investigate this hypothesis has focused on the NAC and striatum, where induction of Δ FosB by addictive drugs depends on their ability to modulate the dopaminergic system.⁶⁰ Interestingly, dopaminergic lesions of the striatum also lead to an increase in Δ FosB expression, suggesting that chronic perturbations of the DA system may induce the protein.⁶¹ Transgenic mice engineered to over-express Δ FosB within striatal regions showed enhanced locomotor sensitization to cocaine and increased conditioned place preference for both cocaine and morphine.^{62,63} These mice also show a greater level of incentive motivation for cocaine in self-administration studies, as indicated by more rapid acquisition of self-administration behavior and higher breakpoints in progressive ratio responding for drug.⁶⁴

In addition to its effects in the striatum, it has recently been observed that repeated administration of cocaine also increases expression of Δ FosB within the OFC of the rat.⁴⁷ Given the role that the OFC is thought to play in mediating 5CSRT and delay-discounting performance, it is therefore plausible that

increased Δ FosB in this region may influence drug-induced changes in task performance. In order to address this question, viral-mediated gene transfer was used to over-express Δ FosB (or the dominant negative protein Δ JunD, which binds to Δ FosB and prevents it from activating gene transcription) within the OFC of animals trained to perform the 5CSRT or delay-discounting task.

Although induction of these proteins did not by itself alter task performance, it did alter the response of these animals to cocaine. In parallel to the effects of repeated administration of cocaine, over-expression of Δ FosB in the OFC significantly attenuated the effects of cocaine on both the 5CSRT and delay-discounting paradigms. Chronic treatment with cocaine further reduced the impact on task performance of an acute cocaine challenge. In contrast, over-expression of Δ JunD within the OFC prevented repeated cocaine treatment from inducing tolerance to the acute effects of cocaine on these tasks. In keeping with the hypothesis suggested above, one interpretation of these findings is that cocaine-induced increases in the expression of Δ FosB within the OFC could reflect part of an adaptive response by the brain to repeated stimulation by cocaine. To reiterate, given that cocaine increases neuronal activity within the OFC,⁶⁵ such a compensatory response could involve upregulation of local inhibitory networks to dampen the excitatory effects of the drug. This would theoretically limit the impact of an acute cocaine challenge on OFC function. In support of this general hypothesis, DNA microarray analysis of tissue taken from the OFC following chronic cocaine treatment revealed an upregulation of GABA_A receptor subunits, substance P, and the mGluR5 receptor, each of which has been shown to dampen cortical activity.^{66–68} Furthermore, these changes were also observed in the OFC following over-expression of Δ FosB, and cocaine's regulation of these genes is blocked by over-expression of Δ JunD.⁴⁷

As postulated above, although adaptations of this kind may preserve cortical function to some extent when drug is on-board, it may also contribute to the cognitive impairments observed after cessation of drug use, potentially by reducing the sensitivity of the OFC to normal levels of stimulation. Preliminary support for this hypothesis has been observed by using the 5CSRT to track the evolution of cognitive changes resulting from daily cocaine self-administration.⁷⁰ 5CSRT testing was carried out Monday–Friday morning, and animals were trained to self-administer cocaine (0.5 mg/kg/infusion) Sunday–Friday afternoons for 2 hours. Initially, animals became more impulsive when learning to self-administer cocaine, but this effect was no longer evident after 4 weeks of training, i.e., the animals grew tolerant to the dyscognitive effects of cocaine. However, when withdrawn from the drug (i.e., rats remained in their homecages and did not self-administer cocaine), animals became significantly more impulsive. Over-expression of Δ FosB within the OFC led to increased premature responding during withdrawal from a period of prolonged cocaine access (6 hours versus 2 hours). These animals

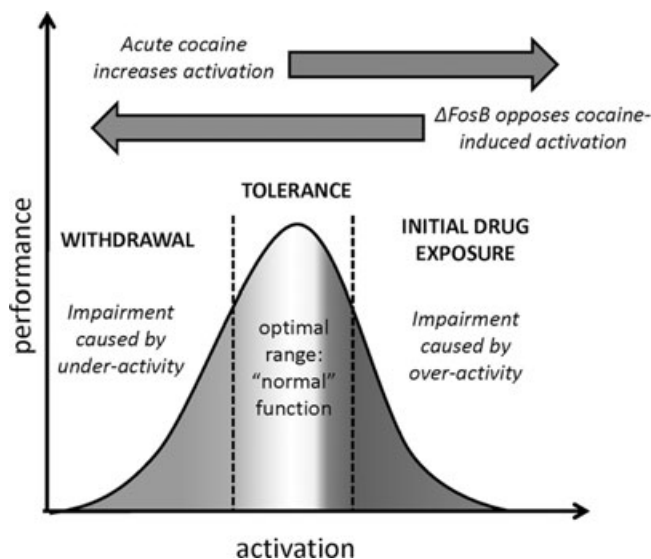


FIGURE 1. Theoretical schematic of how induction of Δ FosB by repeated cocaine administration may alter neuronal activation and cognitive performance within the OFC. Acute cocaine over-stimulates the OFC leading to a decrease in cognitive performance and changes in impulsive behavior. Repeated cocaine exposure leads to adaptive processes within the OFC, potentially including the induction of Δ FosB. This dampens cortical activity in order to counter the excitatory effect of cocaine, leading to tolerance to the cognitive disruption caused by an acute cocaine challenge. However, activation of these inhibitory processes may also lead to under-activation of the OFC during withdrawal, i.e., when cocaine is no longer stimulating cortical activity, leading to a decline in cognitive performance and impairments in impulse control.

also tended to take more of the drug during these longer sessions. Although the dose–response curves were similar in shape to those of control animals, animals over-expressing Δ FosB took more infusions of the highest dose of drug. Interestingly, lesions to the OFC impair rats' ability to regulate their cocaine intake during self-administration sessions, as indicated by an irregular pattern of responding on the drug-paired lever.⁷⁰ Although the temporal profile of responding for cocaine within each session was comparable in both control animals and those over-expressing Δ FosB, the latter appeared less able to regulate their drug intake when the amount of cocaine available was increased.

When these data are integrated together with what is already known about the effects of cocaine on OFC function and activation, the following hypothesis emerges, which is summarized in FIGURE 1. Acute administration of cocaine increases neuronal activity within the OFC. Repeated administration induces expression of Δ FosB, which may reflect or engage an attempt to compensate for this over-stimulation through activation of local inhibitory processes. A

role for Δ FosB in compensating for excessive cortical activation has been suggested previously.⁷¹ If true, increasing Δ FosB expression would essentially adjust the dynamic range of the neural networks in the OFC to account for the acute effects of cocaine treatment. This mechanism would lead to recovery of normal behavioral functioning in OFC-dependent tasks with ongoing drug exposure, as we observed, while also causing a deficit to be unmasked upon sudden cessation of drug exposure. Although the precise effects of increasing Δ FosB on neuronal excitability within the OFC remain to be tested, this model provides a theoretical mechanistic explanation of how repeated activation of the OFC leads to long-term inhibition of this region, and how both processes are inherent in the development of addiction.⁵¹

SUMMARY AND FUTURE DIRECTIONS

Understanding how functioning within the OFC is altered by addictive drugs and the extent to which such changes contribute to cognitive impairments, craving, and relapse is increasingly recognized as a research priority.⁷² Progress on this issue is being made at a number of levels of brain function, including identification of important neural circuits, understanding how different neurotransmitters are involved in regulating relevant behavioral changes, and how these drugs alter processing at the molecular level. Through integrating what is known about the process of addiction at all these levels, it will be possible to obtain a deeper understanding of how addictive drugs alter brain function. Such information may also illuminate questions of how behavior is regulated, both under normal conditions and in other related psychopathologies, such as impulse control disorders.

Reviewing the data presented here from this perspective, it still remains to be determined whether induction of Δ FosB within the OFC is modulated by dopaminergic neurotransmission, in comparison to its expression in the striatum. There are certainly parallels to be observed between the effects of systemic administration of DA D_2 antagonists and the over-expression of Δ FosB within the OFC in that both attenuate the ability of psychostimulant drugs to modulate levels of impulsivity. Little is known regarding the role of 5-HT within the OFC, both in terms of its precise role in regulating impulsivity or drug intake, or in the downstream regulation of cellular processes. Bearing in mind the overlap between the effects of more global dopaminergic and serotonergic manipulations at the behavioral level, it would be interesting if common molecular endpoints could be identified that may explain their redundancy in the regulation of impulse control.

It is becoming clearer that high levels of impulsivity are associated with use of addictive drugs, but whether those who are innately more impulsive are more likely to become addicts, or whether repeated intake of addictive drugs increases impulsivity, is difficult to determine from clinical data. These

two alternatives need not be mutually exclusive. Indeed, bearing in mind that similar areas of the brain are involved in both the regulation of impulsivity and the development of addiction and that both processes are heavily influenced by dopaminergic and serotonergic innervation, it may not be surprising to find that not only can high levels of impulsivity predict use of addictive drugs, but increasing drug intake can also increase levels of impulsivity. Preclinical investigations are starting to reveal that both situations can arise. Improving our understanding of the interaction between impulsivity and addiction could provide the basis for novel avenues of research and therapeutic strategies to target the development of drug dependence.

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