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Abstract

Traditional models of drug abuse emphasize the drug's rewarding effects as reinforcing drug use to the point of physical dependence and addiction. However, the past several years have seen an increased focus on the role of cognitive disturbances both as temporary acute reactions to drugs and as enduring impairments owing to prolonged chronic drug abuse. This chapter focuses on impairments of impulse control and reviews several lines of research that point to the role of impaired control in the development and maintenance of drug abuse disorders. The sections describe how the concept of impaired control is embedded in diagnostic classifications of alcohol abuse disorders and how impaired control characterizes constructs, such as impulsivity and disinhibition, which are key aspects of personalities and psychopathologies commonly associated with drug abuse. Cognitive approaches to the concept of impaired self-control are also examined with the aim of identifying how specific impairments in the ability to inhibit an action can contribute to drug abuse, and possibly emerge as a consequence of prolonged drug abuse. The chapter concludes by highlighting areas for further research, such as gaining a better understanding of the role of deficient inhibitory control in drug abuse for more effective treatment development.

Learning Objectives

- Personality disorders and externalizing disorders that are characterized by impulsive or poorly controlled behaviors are considered risk factors for developing drug abuse disorders.
- Impulsivity and disinhibition are well recognized in diagnostic classifications of drug abuse disorders.
- A basic behavioral characteristic underlying impulsivity and disinhibition appears to be a deficit in the ability to inhibit inappropriate actions.
- CNS depressant drugs, such as alcohol and some psychostimulant drugs, can produce acute impairments of inhibitory control.
- Long-term chronic abusers of drugs display sustained deficits of inhibitory control which could reflect the neural insult owing to prolonged drug exposure.

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Issues that Need to Be Addressed by Future Research

- Research is needed to determine if disinhibition/impulsivity better predicts risks for abuse of specific drugs (e.g., CNS depressants vs. psychostimulants) or if impulsivity represents a risk factor that is nonspecific with regards to types of drugs abused.
- Research needs to explore the possibility that uncontrolled excessive binge use of a drug can arise because of the drug's initial acute disinhibiting effects on the drug-user's behavior.
- Longitudinal studies are needed to understand the causal role of inhibitory control deficits as causal factors and/or behavioral consequences of drug use.
- Impaired self-control could impede the efficacy of drug abuse treatments, and so a better understanding of the role of deficient inhibitory control in drug abuse could help guide more effective treatment strategies.

Drug abuse represents a condition whereby drug-taking and drug-seeking come to dominate behavior to such a degree that drug use appears to usurp control over behavior that was once influenced by normal environmental reinforcers. For many individuals, the pattern of abusive drug use continues despite serious adverse effects and repeated efforts to abstain. The idea that drug abuse represents a loss of self-control has been a long-standing concept in the theory and treatment of addictions, particularly alcohol abuse disorders. Even before the “medicalization” of addiction, society viewed habitual alcohol use as a character flaw whose chief characteristic was a lack of will-power or self-control (e.g., [1]). Early medical accounts by E. M. Jellinek and Mark Keller, who pioneered research on alcoholism, did much to promote the concept of deficient self-control in the etiology of drug abuse [2, 3]. Most notable was Jellinek's notion of a “gamma” alcoholic whose chief, primary symptom was a “loss of control” such that the initial consumption of alcohol triggered an uncontrollable urge to consume more alcohol, leading to a binge. In its strictest interpretation, the loss of control concept failed to gain much empirical support. However, the concept of “reduced” or “impaired” self-control continues today in addiction research and theory. The role of impaired self-control in addiction is studied across a broad range of behavioral investigations, including studies in personality, psychopathology, behavioral neuroscience, and cognitive psychology. Much of the initial work on the etiological role of impaired control in drug abuse disorders concerns its role in alcoholism. As such, much of the theory and research evidence described in this chapter concerns alcohol abuse. The next two sections provide a brief overview of the relevance of impaired control as an important factor in the etiology of

alcohol abuse. The sections describe how the concept of impaired control is embedded in diagnostic classifications of alcohol abuse disorders and how impaired control characterizes constructs, such as impulsivity and disinhibition, which are key aspects of personalities and psychopathologies commonly associated with drug abuse.

Impaired Control as Disinhibited Personality and Psychopathology

Much of the evidence for the involvement of impaired control in drug abuse has come from studies on personality [4]. This area of research has focused on broad-based personality traits generally labeled as “impulsivity” or “disinhibition.” These traits refer to a pattern of under-controlled behavior in which the individual lacks the ability to delay gratification and acts without forethought or consideration of potential consequences. The traits are typically assessed by self-report instruments, some of which are designed specifically to assess the impulsivity-disinhibition trait, such as the Barratt Impulsivity Scale and the Eysenck Impulsivity Scale [5, 6]. The traits are also assessed by comprehensive personality inventories, such as the NEO-Five Factor Inventory [7], in which impulsivity-disinhibition is comprised within major dimensions of personality (e.g., extroversion, openness to experience).

Studies using these types of instruments have demonstrated reliable associations between impulsivity-disinhibition and drug use. Much of this work has concerned the relation between these traits and alcohol use. Studies find that impulsive or disinhibited individuals tend to drink more frequently and in larger amounts during drinking episodes [8–10]. Impulsive individuals are also more likely to binge drink [11]. That is, drink to the point of intoxication. Not surprisingly then, impulsivity and disinhibition also have been linked to actual substance and alcohol use disorders. For example, abusers of illicit drugs and individuals diagnosed with alcoholism tend to score higher on measures of impulsivity, disinhibition, and related traits, such as sensation-seeking [12–14]. Moreover, there is growing evidence that impulsivity might play an important causal role in drug abuse. Prospective studies have shown that impulsive characteristics often precede the onset of problem alcohol use. Longitudinal studies of children and adolescents have shown that impulsivity predicts early-onset drinking age and development of heavy drinking and alcohol dependence in young adults [15, 16]. Heritability studies of substance use disorders also point to the involvement of impulsivity-disinhibition. For example, studies of individuals with a familial risk for substance use disorder, such as children of alcoholics, find that these individuals also display increased impulsivity-disinhibition [17, 18].

Alcohol and other drug abuse disorders are considered by many investigators to be symptomatic of some disinhibitory psychopathology [4, 19–21]. This argument is based on findings from studies examining drug abuse in relation to impulsivity-disinhibition as a central characteristic of a psychopathology. For example, several studies have examined the link between DSM personality disorder clusters and drug abuse. The general finding from this research is that substance abuse disorders have a high comorbidity with cluster B personality disorders. This cluster includes antisocial, borderline, and histrionic disorders, which are all characterized by under-controlled, disinhibited, and impulsive patterns of behavior. By contrast, cluster type A “odd-eccentric” (e.g., schizotypal disorders) and cluster type C “anxiety-related” (e.g., obsessive-compulsive disorder) fail to demonstrate consistent relationships with substance use [14]. It is also well established that externalizing disorders in childhood and adolescence, such as Attention Deficit/Hyperactivity Disorder (ADHD) and Conduct Disorder (CD), also pose risk for developing substance abuse disorders [22–27]. Studies of adults with ADHD find lifetime rates of alcohol abuse disorders ranging between 21% and 53% [28, 29]. A hallmark characteristic of ADHD is disinhibited or under-controlled behavior. Accordingly, there is also growing suspicion that such disinhibition might be the common, core deficit of these disorders that mediates their risk potential for adolescent drug use [30].

Impaired Control in Diagnostic Criteria for Alcohol Abuse Disorders

Impaired or deficient self-control is also a criterion for diagnostic classifications of alcoholism. Early on it was recognized that alcoholism was a heterogeneous disorder. That is, alcoholics differed in their patterns of abusive drinking. For example, it was recognized that some alcoholics drink daily, never appear drunk or intoxicated, but would likely experience withdrawal effects should they stop drinking. By contrast, other drinkers would go days or even weeks without drinking, but once they began drinking, they drank excessively to the point of gross inebriation or loss of consciousness. For Jellinek, these two patterns of drinking behavior represented two different “species” of alcoholic [31]. Jellinek labeled the former species, “delta” and the latter, “gamma.” The delta alcoholic drinks daily, is likely physically dependent, but can control the amount consumed during the drinking episode (i.e., does not binge drink). Aside from an inability to abstain from alcohol, this alcoholic functions well in society. In contrast, the gamma alcoholic appears able to abstain from alcohol for long periods of time, but once consumption begins, this alcoholic loses control over intake and drinks to excess (i.e., binges). Thus, a critical

distinction between these two primary typologies in Jellinek’s schema is the aspect of drinking behavior for which the alcoholic has no control over: control over when to drink versus control over how much to drink.

The concept of impaired control continued to play a key role in later diagnostic classifications of alcoholism, whose typologies are still commonly used today. For example, based on prospective adoption studies, Cloninger [19] offered a genetic-based dichotomous classification of alcoholism: Type I and Type II. Type I alcoholics are said to drink primarily to relieve stress or negative effect, often referred to as “relief drinking.” These individuals develop their abusive drinking patterns later in life (i.e., after age 25). They also continue to function fairly well, both vocationally and interpersonally. These drinkers are sometimes casually referred to as “functioning alcoholics.” By contrast, Type II alcoholics demonstrate abusive drinking patterns early, before the age of 25, are typically male, are unable to abstain from alcohol for any extended period, and are physically dependent. Moreover, the Type II alcoholic is characterized by under-controlled, antisocial, or disinhibited behavior, especially during a drinking episode. This lack of controlled behavior often results in social and legal problems for the individual. Unlike Jellinek’s early system, Cloninger’s later classification scheme benefited from advances in personality assessment and application of DSM-based symptom criteria to establish evidence for under-controlled behavior. As such, the lack of control demonstrated in the Type II alcoholic was largely evident by the fact that these drinkers commonly met symptom criteria for comorbid diagnoses of antisocial personality disorder or conduct disorder. Similar to Cloninger’s dichotomy, Babor described a distinction between Type A and Type B alcoholics [32]. Like Cloninger’s Type I alcoholics, Type A alcoholics demonstrate a late onset of abusive drinking, have few social or legal problems, and show little or no comorbid psychopathology. Type B alcoholics resemble Cloninger’s Type II alcoholic, in that these drinkers develop alcohol problems early on and tend to have a history of antisocial and conduct problems.

Based on the diagnostic classification systems described here, it is apparent that the concept of impaired control has played an important role in characterizing the heterogeneity of alcohol abuse disorders since the first systematic classification scheme offered by Jellinek. It is also important to note that the basic classification dichotomies of Cloninger and Babor have been successfully applied to other drug abuse as well (e.g., cocaine), suggesting that impaired self-control could be an important characteristic for subtyping drug abuse in general [33]. Although diagnostic typologies are sometimes criticized in favor of dimensional models of psychopathology and substance use disorders [34], such classification schemes are useful because they highlight groups or clusters of symptoms (e.g., impaired control, physical dependence) that

could have a common etiology. With respect to disinhibition, the alcoholism subtypes characterized by this trait appear to represent the more severe form of alcoholism. Moreover, this behavioral characteristic could have a strong genetic component as evident by its association with early-onset drinking problems and comorbid psychopathology [35]. With regard to treatment, the recognition of distinct typologies enables treatments to be tailored specifically to the particular symptoms and behavioral problems in each subtype. For many behaviorally based alcohol interventions, the presence of disinhibited or under-controlled behavior is a key symptom area of behavioral management in the treatment of the disorder. As such, typology-specific diagnoses could aid in matching patients to specifically tailored treatment programs.

In sum, impulsivity-disinhibition is well recognized in diagnostic typologies for substance use disorders. Studies of personality and psychopathology provide compelling evidence for a link between disinhibition and substance abuse. The involvement of disinhibition is evident from studies of normal personality (i.e., trait impulsivity) and studies of impulsivity-disinhibition as expressed through externalizing disorders (e.g., ADHD) or personality disorders (e.g., antisocial personality disorder). From this research, several new questions have arisen in recent years. One question concerns the possibility that certain expressions of the impulsivity-disinhibition could be associated with risks for particular types of drug use (e.g., alcohol vs. stimulant abuse). For example, Flory et al. [23] found that extroversion was a stronger predictor of alcohol use, whereas openness to experience better predicted marijuana use. Others have also found some evidence for specificity between particular personality traits and the type of drug use they predict [36]. Another issue that has received considerable attention concerns the degree to which antisocial behavior accounts for much of the relationships between personality traits and drug abuse. Unquestionably, antisocial behavior is one of the strongest predictors of risk for drug abuse. As such, many investigators are concerned with the possibility that associations between certain personality traits with drug use might simply be accounted for by antisocial behavior [36–38]. Isolating the specific influence of antisocial behavior from personality traits is a major aim of current research.

Impaired Control as Deficient Response Inhibition

Although it is important to characterize the behavioral correlates of drug abuse in terms of complex traits and personality, there is also a need to identify specific behavioral mechanisms by which these traits might promote drug abuse. In particular, it is important to understand the basic

behavioral mechanisms that underlie disinhibited or impulsive behavior. Cognitive neuroscience approaches the concept of impaired self-control with the aim of identifying and characterizing the basic neurocognitive mechanisms that underlie the regulation of behavior [39, 40]. Unlike personality or broad-based trait approaches, this approach breaks down these constructs to study their component mechanisms and identify disturbances in the basic “building blocks” of behavior. This section reviews some cognitive models that focus on inhibitory mechanisms of behavior and describes their current use in the study of drug abuse.

Behaviors are instigated or motivated by a host of factors, including internal states, such as hunger, and by external events, such as the rich array of environmental cues that signal biologically relevant stimuli (e.g., primary and secondary reinforcers). Without any means to control responses to these signals, an organism’s behavior would be immediately responsive and completely determined by such events. However, it is widely recognized that higher organisms, such as humans and other mammals, can exert control over behavioral output to either delay, alter, or completely inhibit environmentally instigated responses. Several theories in cognitive neuroscience postulate that the control of behavior is governed by distinct inhibitory and activational systems [41–48].

Considerable research has focused on inhibitory mechanisms of behavioral control. This ability is thought to involve frontal lobe substrates that exert inhibitory influences over conditioned responses and reflexive behaviors [42, 43]. Studies in neuropharmacology and neuroanatomy have identified distinct neural systems that implicate separate inhibitory and activational mechanisms in the control of behavior [30, 49–51]. The orbitofrontal and medial prefrontal cortex contain neural substrates that subserve many ongoing activities that control and regulate behavior. The ability to inhibit or suppress an action enhances the organism’s behavioral repertoire by affording it some control over when and where responses may be expressed. As such, the inhibition of behavior is an important function that sets the occasion for many other activities that require self-restraint and regulation of behavior. Not surprisingly then, deficient or impaired inhibitory control has been implicated in the display of impulsivity and disorders of self-control. Aggressive and impulsive behaviors that characterize disorders, such as antisocial personality, obsessive–compulsive, and ADHD, have been attributed to impaired inhibitory mechanisms [22, 52].

In recent years, several “model-based” assessments of inhibitory mechanisms have been used to characterize drug abusers (for a review, see [30, 53]). Stop-signal and cue/no-go models evaluate control as the ability to activate and to inhibit prepotent (i.e., instigated) responses [45, 54, 55]. The tasks model behavioral control using a reaction time scenario that measures the countervailing influences of inhibitory and activational mechanisms. Individuals are required to quickly

activate a response to a go-signal and to inhibit a response when a stop-signal occasionally occurs. Activation is typically measured as the speed of responding to go-signals and inhibition to stop-signals is assessed by the probability of suppressing the response or by the time needed to suppress the response. In these models, inhibition of a response is usually required in a context in which there is a strong tendency to respond to a stimulus (i.e., a prepotency), thus making inhibition difficult. The validity of these models is well documented. The models are sensitive to inhibitory deficits characteristic of brain injury [56, 57], trait-based impulsivity [58], and self-control disorders, such as ADHD [59–61].

Acute Drug-Induced Impairment of Inhibitory Control

Several recent studies using these tasks have provided consistent evidence that moderate doses of CNS depressant drugs, such as alcohol and benzodiazepines, selectively reduce the user's ability to inhibit behavior at doses that leave the ability to activate behavior relatively unaffected [62–66]. For example, Fillmore and Weafer [67] used a cued go no-go task to test the impairing effect of alcohol on drinkers' inhibitory control over their behavioral impulses. The cued go no-go task presented go and no-go targets to which subjects had to execute a response (go) or inhibit the response (no-go). Subjects' inhibitory control was tested on two occasions: following a placebo and following an active dose that was sufficient to raise a drinker's BAC to 0.08%. Compared with placebo, alcohol impaired inhibitory control by increasing the likelihood that drinkers would fail to inhibit responses to no-go targets. By contrast, no effect of alcohol at this dose was observed on the ability of drinkers to execute the responses to go targets as measured by their speed of responding.

What is particularly remarkable about findings such as these is the robust impairment that is evident in spite of the relatively simple nature of the inhibitory response tested. Typically, sensitivity to alcohol-induced impairment increases as a function of dose and task complexity [68]. However, the impairing effects of alcohol on the ability to inhibit behavior are often observed at blood alcohol concentrations at or below 0.08% [30]. The findings suggest that activities that require quick suppression of actions might be particularly vulnerable to the disruptive influences of alcohol.

In addition, alcohol-induced impairments of inhibitory mechanisms might actually exert considerable disruptive influence on higher-order, executive cognitive functions. Many fundamental cognitive and perceptual processes, such as inhibitory mechanisms, are considered to operate in a "bottom-up" fashion to exert increasing influence at each stage of higher-order attentional and cognitive functions. Thus, the alcohol-induced disturbances of basic control

mechanisms, such as inhibitory processes, might actually result in much more pronounced impairments of the higher cognitive operations for which they serve (e.g., decision-making, planning, and goal maintenance).

The findings might also provide some account for the long-standing observation that alcohol intoxication is often characterized by increased impulsivity and aggression. Using the same types of tasks as those described here, deficits of inhibitory control have been identified in individuals with disorders characterized by aggressive or impulsive behaviors, such as ADHD and antisocial personality [22, 52]. In fact, the acute impairments of inhibitory control that are produced by alcohol closely resemble those inhibitory deficits that are assumed to be symptomatic of externalizing disorders [53]. This raises an intriguing possibility that alcohol temporarily disrupts cognitive functioning in a manner similar to the enduring cognitive disturbances that are characteristic of disorders, such as ADHD.

Evidence for the vulnerability of inhibitory mechanisms to alcohol effects also could offer important new insights into the development and maintenance of alcohol abuse. Although there is little dispute that reward mechanisms play an important role in abuse potential, the acute cognitive impairing effects of alcohol might also contribute to abuse by compromising mechanisms involved in the regulation and self-control of behavior and attention [30, 53]. In particular, inhibitory mechanisms likely play an important role in terminating alcohol use during an episode [30, 51, 53]. Many drinkers report intentions to limit their alcohol use to one or two drinks only to fail and instead drink excessively [69]. Such accounts have fueled the notion that alcohol reduces control over consumption in some individuals. Terminating a drinking episode requires inhibition of ongoing alcohol-administration behaviors and the reallocation of attention away from alcohol-related stimuli. Any impairment of normal inhibitory mechanisms resulting from an initial dose of alcohol could compromise the ability to stop additional alcohol administrations in a drinking situation. Thus, acute alcohol-induced impairment of inhibitory processes could represent an important behavioral mechanism by which an initial alcohol dose promotes subsequent self-administration. In fact, laboratory studies find that increased sensitivity to the acute disinhibiting effects of alcohol predicts heavy alcohol use in both humans [70] and laboratory animals [71].

Studies of inhibitory control have also examined the acute effects of psychostimulant drugs. Studies using stop-signal and cued go/no-go tasks have found that the stimulants, methylphenidate and D-amphetamine, can improve inhibitory control in children with ADHD and in healthy adults [72, 73]. It has been suggested that illicit use of the commonly abused stimulants, cocaine and amphetamine, might be motivated in part by a desire to self-medicate attentional deficits and hyperactive/impulsive tendencies (e.g., [74, 75]).

Drug-induced enhancement of inhibitory control might contribute to abuse potential by representing a desirable effect for the user that reinforces their use of stimulant drugs. However, evidence for facilitatory effects on inhibitory control is not entirely consistent. Some studies of cocaine and D-amphetamine have failed to demonstrate facilitatory effects on inhibitory control. In fact, studies of orally administered doses of cocaine HCl (50–150 mg) and D-amphetamine (5–20 mg) actually produced slight impairments of inhibitory control in stimulant abusers, as evidenced by a decreased ability to inhibit responses [76, 77]. However, in a study of adults with no history of stimulant abuse, D-amphetamine was found to have no effect on inhibitory control [78].

One factor that might be critical in determining facilitation of inhibitory control is dose. Some studies of methylphenidate in children with ADHD have reported U-shaped dose–response curves following methylphenidate [73, 79, 80]. In these studies methylphenidate improved children's inhibitory control in a dose-dependent fashion up to a point at which higher doses failed to produce any improvement. A study of adult stimulant drug abusers revealed a similar U-shaped dose–response curve in response to cocaine [81]. Lower doses of cocaine improved the subjects' inhibitory control but no beneficial effects of the drug were observed at higher doses. One speculation is that the facilitating effects of stimulant drugs on inhibitory control are limited to a range of intermediate doses, above which improvement is no longer evident and impairing effects could possibly emerge. Such a two-phasic dose–response function has implications for understanding how changes in inhibitory control could contribute to the abuse of stimulant drugs. An initial stimulant dose (i.e., a “rock” of cocaine) could restore or possibly enhance cognitive functioning. Moreover, such facilitation might represent a sought-after, restorative effect for the user. But, as additional doses are administered, inhibitory control could become impaired as brain levels increase, leading to behavioral impulsivity, perseverative responses, and possibly binge use of the drug.

Neuropsychological and brain imaging studies of cocaine users support a basic tenet of the restorative hypothesis, namely evidence of basal deficits in inhibitory control [30]. Compared with healthy controls, cocaine abusers show patterns of premature responding [82, 83] and perseverative behavior [84]. Brain imaging studies find evidence of hypoactivity in the cingulate and dorsolateral prefrontal cortical regions [85, 86] which are areas associated with inhibitory control of prepotent actions [87, 88]. The hypoactivity in these regions could reflect damage owing to long-term cocaine use [89, 90]. Recent studies of cocaine users also show enhanced sensitivity to stimulant drugs in these brain regions (i.e., heightened activation), possibly resulting from long-term cocaine abuse [91]. Such supersensitivity could lead to disinhibited or impulsive behavior in response to higher drug doses.

Chronic Drug-Induced Impairment of Inhibitory Control

As mentioned above, there is evidence that prolonged, chronic use of an abused drug, such as cocaine, can alter neural functioning, possibly leading to relatively permanent impairments of the user's cognitive abilities. Several studies have compared the neuropsychological test performance of chronic drug abusers to comparison controls (for reviews, see [49, 92, 93]). Much of this work has focused on alcoholics and abusers of stimulant drugs, such as cocaine and methamphetamine. With regard to alcohol, it has long been known that chronic abuse can result in sustained memory impairments, with the most severe form being Korsakoff's Syndrome. Currently, it is now recognized that prolonged abuse of alcohol is associated with widespread neuropsychological deficits, involving memory, attention, learning, problem solving, and perceptual motor speed [94–97]. Similarly, studies of stimulant abusers also demonstrate many of the same types of neuropsychological deficits [98]. Moreover, the deficits evident in these drug abusers do not appear to be acute effects of recent drug use, or acute withdrawal symptoms, because they have been shown to persist in detoxified, abstinent individuals for at least 1 year [99].

In addition to demonstrating general impairments in attention, memory and other global functions, more recent research has identified specific deficits in the inhibitory control of drug abusers. Studies using the stop-signal and cued go/no-go tasks find that cocaine users display deficits in the ability to inhibit responses, but no impairment in the ability to activate such behavior [100, 101]. Studies of abstinent alcoholics in treatment also find some evidence for deficient inhibitory control on the go/no-go task, which is most evident in the Type II subtype [102, 103].

It is important to recognize that such cross-sectional comparisons between drug abusers and control samples cannot establish a causal link between drug use and deficits of inhibitory control. Nonetheless, there are lines of evidence that suggest that such deficient inhibitory control among drug abusers could be due, in part, to prolonged exposure to abused drugs. First, the degree of inhibitory deficit is often related to the severity of drug abuse, such that those who have abused drugs more frequently, or for longer periods, tend to display the greatest deficits (e.g., [83, 104, 105]). Second, considerable work in neuroimaging has shed light on how drug abuse can alter neural systems underlying many neuropsychological functions, including inhibitory control [49, 106]. This approach examines both the neural changes that occur in response to the acute administration of an abused drug and the difference in neural functioning between drug abusers and healthy controls, presumably as a consequence of prolonged exposure. Much of this work examines

individuals with histories of polydrug abuse (i.e., cocaine and alcohol abuse). The general aim of this approach is to understand how the neural responses to acute drug administration can eventually lead to permanent changes in neural functioning as a function of repeated drug use. Positron emission tomography (PET) and functional neural imaging techniques of polydrug abusers reveal altered dopamine functioning in brain areas associated with inhibitory control, such as the orbitofrontal cortex and cingulate gyrus [49, 51, 101, 106]. Impaired cognitive functions, such as reduced inhibitory control over approach behaviors, might result from a supraactivation of cortical D1-like receptor systems. A current working hypothesis is that individuals initially display elevated increases in dopamine (i.e., supraactivation) following drug use which, over repeated use, leads to neural adaptations that results in diminished dopaminergic activity in brain regions, leading to increased motivation for drugs and diminished impulse control [106].

A final line of evidence for a causal role between drug use and deficient inhibitory control comes from preclinical studies of laboratory animals. Studies of laboratory animals allow for a longitudinal approach in which neural and behavioral changes can be assessed before and following chronic exposure to a drug (for a review, see [107]). Preclinical studies provide considerable evidence for enduring neural and behavioral changes following chronic exposure to drugs. This body of literature is extensive and beyond the scope of this review. However, with regard to inhibitory control, studies of animals find that neural systems associated with inhibitory control are particularly vulnerable to neurotoxic insults from drug exposures, especially during critical developmental stages (e.g., [108]).

In sum, some interesting parallel effects have emerged in studies of acute and chronic drug effects on inhibitory control. As an acute reaction, an impaired ability to inhibit inappropriate responses has become well documented in response to some CNS depressant drugs, most notably, alcohol. It also appears that stimulant drugs, such as cocaine, are capable of reducing inhibitory control as an acute reaction, however, such effects might depend on the dose and the user's prior drug history. In terms of chronic use, several lines of evidence suggest that repeated abuse of stimulant drugs and alcohol can produce enduring changes in neural functioning that result in sustained deficits of impulse control.

Future Directions and Considerations

Traditional models of drug abuse emphasize the drug's rewarding effects as reinforcing drug use to the point of physical dependence and addiction. However, the past several years has seen an increased focus on the role of cognitive disturbances both as temporary acute reactions to drugs

and as enduring impairments owing to prolonged chronic drug abuse. This chapter focused on impairments of impulse control and reviewed several lines of research that point to the role of impaired control in the development and maintenance of drug abuse disorders. There is considerable agreement among these lines of research that impaired self-control plays an important role in the risk for developing drug abuse disorders.

Cross-sectional identification of specific inhibitory deficits that may contribute to, or result from drug use will lay the foundation for longitudinal studies of drug use that track changes in inhibitory functioning in relation to drug use over time. Inhibitory deficits might directly contribute to the initiation of drug use, and thus operate as a specific behavioral risk factor. At the same time, inhibitory deficits might also arise as a result of neural insult owing to prolonged drug abuse. In such a case, inhibitory mechanisms might recover over a period of abstinence. Some research has already begun to examine changes in neuropsychological test performance as a function of varying periods of drug abstinence (e.g., [109]). Abstinence effects on specific inhibitory deficits have yet to be examined. Long-term observation of detoxified individuals could provide important information on the persistence of these deficits.

Finally, evidence for the involvement of impaired self-control also poses particular challenges for drug abuse treatment development, as treatment researchers come to recognize that poor impulse control and impaired cognitive functions, in general, can undermine the efficacy of many behaviorally based treatments. A better understanding of the role of deficient inhibitory control in drug abuse could help guide the development of pharmacological treatments for drug abuse as well. A sought-after effect of many candidate pharmacotherapies for drug abuse is the reduction of subjectively rewarding states produced by the drug. The concomitant disruption of neurocognitive control mechanisms has been afforded less attention as a mechanism of abuse. The possibility that some pharmacotherapies might operate to reduce drug use by strengthening inhibitory control has yet to be examined.

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References

1. McCorkindale I. The Canadian lesson book on temperance and life. Toronto: Dominion Scientific Temperance Committee; 1926.
2. Jellinek EM. Current notes—phases of alcohol addiction. *Q J Stud Alcohol*. 1952;13:673–84.

3. Keller M. On the loss of control phenomenon in alcoholism. *Br J Addict.* 1972;67:153–66.
4. Widiger TA, Smith GT. Substance use disorder: abuse, dependence and dyscontrol. *Addiction.* 1994;89:267–82.
5. Eysenck SB, Pearson PR, Easting G, Allsopp JF. Age norms for impulsiveness, venturesomeness, and empathy in adults. *Personal Individ Differ.* 1985;6:613–9.
6. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol.* 1995;51:768–74.
7. Costa PT, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) professional manual. *Obessa, FL: Psychological Assessment Resources; 1992.*
8. Cherpitel CJ. Alcohol, injury, and risk-taking behavior: data from a national sample. *Alcohol Clin Exp Res.* 1993;17:762–6.
9. Goudriaan AE, Grekin ER, Sher KJ. Decision making and binge drinking: a longitudinal study. *Alcohol Clin Exp Res.* 2007;31:928–38.
10. Simons JS. Differential prediction of alcohol use and problems: the role of biopsychosocial and social-environmental variables. *Am J Drug Alcohol Abuse.* 2003;29:861–79.
11. Marczinski CA, Combs SW, Fillmore MT. Increased sensitivity to the disinhibiting effects of alcohol in binge drinkers. *Psychol Addict Behav.* 2007;21:346–54.
12. Bergman B, Brismar B. Hormone levels and personality traits in abusive and suicidal male alcoholics. *Alcohol Clin Exp Res.* 1994;18:311–6.
13. Sher KJ, Trull TJ, Bartholow BD, Vieth A. Personality and alcoholism: issues, methods, and etiological processes. In: Blane H, Leonard E, editors. *Psychological theories of drinking and alcoholism.* New York: Plenum; 1999. p. 54–105.
14. Trull TJ, Waudby CJ, Sher KJ. Alcohol, tobacco, and drug use disorders and personality disorder symptoms. *Exp Clin Psychopharmacol.* 2004;12:65–75.
15. August GJ, Winters KC, Realmuto GM, Fahnhorst T, Botzet A, Lee S. Prospective study of adolescent drug use among community samples of ADHD and non-ADHD participants. *J Am Acad Child Adolesc Psychiatry.* 2006;45:824–32.
16. Ernst M, Luckenbach DA, Moolchan ET, Leff MK, Allen R, Eshel N, London ED, Kimes A. Behavioral predictors of substance-use initiation in adolescents with and without attention-deficit/hyperactivity disorder. *Pediatrics.* 2006;117:2030–9.
17. Alterman AI, Bedrick J, Cacciola JS, Rutherford MJ, Searles JS, McKay JR, Cook TG. Personality pathology and drinking in young men at high and low familial risk for alcoholism. *J Stud Alcohol.* 1998;59:495–502.
18. Sher KJ. *Children of alcoholics: a critical appraisal of theory and research.* Chicago: University of Chicago Press; 1991.
19. Cloninger CR. Recent advances in family studies of alcoholism. *Prog Clin Biol Res.* 1987;241:47–60.
20. Finn PR, Kessler DN, Hussong AM. Risk for alcoholism and classical conditioning to signals for punishment: evidence for a weak behavioral inhibition system? *J Abnorm Psychol.* 1994;103:293–301.
21. Sher KJ, Trull TJ. Personality and disinhibitory psychopathology: alcoholism and antisocial personality disorder. *J Abnorm Psychol.* 1994;103:92–102.
22. Barkley R. *Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment.* 3rd ed. New York: Guilford; 2006.
23. Flory K, Milich R, Lynam DR, Leukefeld C, Clayton R. Relation between childhood disruptive behavior disorders and substance use and dependence symptoms in young adulthood: Individuals with symptoms of attention-deficit/hyperactivity disorder and conduct disorder are uniquely at risk. *Psychol Addict Behav.* 2003;17:151–8.
24. Flory K, Lynam DR. The relation between attention deficit hyperactivity disorder and substance abuse: what role does conduct disorder play? *Clin Child Fam Psychol Rev.* 2003;6:1–16.
25. Hartung CM, Milich R, Lynam DR, Martin CA. Understanding the relations among gender, disinhibition, and disruptive behavior in adolescents. *J Abnorm Psychol.* 2002;111:659–64.
26. Molina BSG, Smith BH, Pelham WE. Interactive effects of attention deficit hyperactivity disorder and conduct disorder on early adolescent substance use. *Psychol Addict Behav.* 1999;13:348–58.
27. Molina BSG, Pelham WE, Gnagy EM, Thompson AL, Marshal MP. Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcohol Clin Exp Res.* 2007;31:643–54.
28. Barkley RA, Murphy KR, Kwasnik D. Motor vehicle driving competencies and risks in teens and young adults with attention deficit hyperactivity disorder. *Pediatrics.* 1996;98:1089–95.
29. Biederman J. Impact of comorbidity in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* 2004;65:3–7.
30. Fillmore MT. Drug abuse as a problem of impaired control: current approaches and findings. *Behav Cogn Neurosci Rev.* 2003;2:179–97.
31. Jellinek EM. *The disease concept of alcoholism.* New Brunswick, NJ: Hillhouse; 1960.
32. Babor TF, Hofmann M, DelBoca FK, Hesselbrock VM, Meyer RE, Dolinsky ZS, Rounsaville B. Types of alcoholics: I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Arch Gen Psychiatry.* 1992;49(8):599–608.
33. Ball SA, Carroll KM, Babor TF, Rounsaville BJ. Subtypes of cocaine abusers: support for a type A-type B distinction. *J Consult Clin Psychol.* 1995;63:115–24.
34. Widiger TA, Trull TJ. Plate tectonics in the classification of personality disorder: shifting to a dimensional model. *Am Psychol.* 2007;62:71–83.
35. Hesselbrock VM, Hesselbrock MN. Are there empirically supported and clinically useful subtypes of alcohol dependence? *Addiction.* 2006;101 Suppl 1:97–103.
36. Grekin ER, Sher KJ, Wood PK. Personality and substance dependence symptoms: modeling substance-specific traits. *Psychol Addict Behav.* 2006;20(4):415–24.
37. Miller JD, Lynam DR. Psychopathy and the Five-factor model of personality: a replication and extension. *J Personal Assess.* 2003;81:168–78.
38. Lynam DR, Leukefeld C, Clayton RR. The contribution of personality to the overlap between antisocial behavior and substance use/misuse. *Aggress Behav.* 2003;29(4):316–31.
39. Goschke T. Voluntary action and cognitive control from a cognitive neuroscience perspective. In: Massen S, Prinz W, Roth G, editors. *Voluntary action: brains, minds, and sociality.* New York, NY: Oxford University Press; 2003. p. 49–85.
40. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* 2001;24:167–202.
41. Fox E. Negative priming from ignored distractors in visual selection: a review. *Psychonomic Bull Rev.* 1995;2:145–73.
42. Fowles DC. Application of a behavioral theory of motivation to the concepts of anxiety and impulsivity. *J Res Personal.* 1987;21:417–35.
43. Gray JA. The behavioral inhibition system: a possible substrate for anxiety. In: Feldman MP, Broadhurst A, editors. *Theoretical and experimental bases of behavior therapies.* London: Wiley; 1976. p. 3–41.
44. Gray JA. Drug effects of fear and frustration. Possible limbic site of action of minor tranquilizers. In: Iverson LL, Iverson SD, Snyder SH, editors. *Handbook of psychopharmacology, vol. 8.* New York: Plenum; 1977. p. 433–529.
45. Logan GD, Cowan WB. On the ability to inhibit thought and action: a theory of an act of control. *Psychological Review.* 1984;91:295–327.
46. May CP, Kane MJ, Hasher L. Determinants of negative priming. *Psychol Bull.* 1995;118:35–54.

47. Patterson CM, Newman JP. Reflectivity and learning from aversive events: toward a psychological mechanism for the syndromes of disinhibition. *Psychol Rev.* 1993;100:716–36.
48. Quay HC. Inhibition and attention deficit hyperactivity disorder. *J Abnorm Child Psychol.* 1997;25:7–13.
49. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implication for the control of behavior by reward-related stimuli. *Psychopharmacology.* 1999;146:373–90.
50. Leigh RJ, Zee DS. The neurology of eye movements. 3rd ed. New York: Oxford University Press; 1999.
51. Lyvers M. “Loss of control” in alcoholism and drug addiction: a neuroscientific interpretation. *Exp Clin Psychopharmacol.* 2000;8: 225–49.
52. Nigg JT. What causes ADHD? Understanding what goes wrong and why. New York: Guilford; 2006.
53. Fillmore MT. Acute alcohol-induced impairment of cognitive functions: past and present findings. *Int J Disabil Hum Dev.* 2007;6: 115–25.
54. Logan GD. On the ability to inhibit thought and action: a user’s guide to the stop-signal paradigm. In: Dagenbach D, Carr TH, editors. *Inhibitory processes in attention, memory, and language.* San Diego, CA: Academic; 1994.
55. Miller J, Schaffer R, Hackley SA. Effects of preliminary information in a go versus no-go task. *Acta Psychol.* 1991;76:241–92.
56. Cremona-Meteyard SL, Geffen GM. Event-related potential indices of visual attention following moderate to severe closed head injury. *Brain Injury.* 1994;8:541–58.
57. Malloy P, Bihrele A, Duffy J, Cimino C. The orbitomedial frontal syndrome. *Arch Clin Neuropsychol.* 1993;8:185–201.
58. Logan GD, Schachar RJ, Tannock R. Impulsivity and inhibitory control. *Psychol Sci.* 1997;8(1):60–4.
59. Tannock R. Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. *J Child Psychol Psychiatry.* 1998;39:65–99.
60. Oosterlaan J, Sergeant JA. Inhibition in ADHD, aggressive, and anxious children: a biologically based model of child psychopathology. *J Abnorm Child Psychol.* 1996;24:19–37.
61. Schachar R, Tannock R, Marriott M, Logan G. Deficient inhibitory control in attention deficit hyperactivity disorder. *J Abnorm Child Psychol.* 1995;23:411–37.
62. de Wit H, Crean J, Richards JB. Effects of d-amphetamine and ethanol on a measure of behavioral inhibition in humans. *Behav Neurosci.* 2000;114:830–7.
63. Fillmore MT, Rush CR, Kelly HK, Hays L. Triazolam impairs inhibitory control of behavior in humans. *Exp Clin Psychopharmacol.* 2001;9:363–71.
64. Fillmore MT, Vogel-Sprott M. An alcohol model of impaired inhibitory control and its treatment in humans. *Exp Clin Psychopharmacol.* 1999;7:49–55.
65. Mulvihill LE, Skilling TA, Vogel-Sprott M. Alcohol and the ability to inhibit behavior in men and women. *J Stud Alcohol.* 1997;58: 600–5.
66. Marcinski CA, Fillmore MT. Pre-response cues reduce the impairing effects of alcohol on the execution and suppression of responses. *Exp Clin Psychopharmacol.* 2003;11:110–7.
67. Fillmore MT, Weafer J. Alcohol impairment of behavior in men and women (Target Article). *Addiction.* 2004;99:1237–46.
68. Maylor EA, Rabbitt PM, James GH, Kerr SA. Effects of alcohol, practice, and task complexity on reaction time distributions. *Q J Exp Psychol Hum Exp Psychol.* 1992;49:119–39.
69. Collins RL. Drinking restraint and risk for alcohol abuse. *Exp Clin Psychopharmacol.* 1993;1:44–54.
70. Weafer J, Fillmore MT. Individual differences in acute alcohol impairment of inhibitory control predict ad libitum alcohol consumption. *Psychopharmacology.* 2008;201(3):315–24.
71. Poulos CX, Parker JL, Le DA. Increased impulsivity after injected alcohol predicts later alcohol consumption in rats: evidence for ‘loss-of-control drinking’ and marked individual differences. *Behav Neurosci.* 1998;112(5):1247–57.
72. de Wit H, Engasser JL, Richards JB. Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology.* 2002;27(5):813–25.
73. Tannock R, Schachar R, Logan G. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. *J Abnorm Child Psychol.* 1995;23:235–67.
74. Khantzian E. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry.* 1985;142:1259–64.
75. Schiffer F. Psychotherapy of nine successfully treated cocaine abusers: techniques and dynamics. *J Subst Abuse Treat.* 1988; 5:131–7.
76. Fillmore MT, Rush CR, Hays L. Acute effects of oral cocaine on inhibitory control of behavior in humans. *Drug Alcohol Depend.* 2002;67:157–67.
77. Fillmore MT, Rush CR, Marcinski CA. Effects of d-amphetamine on behavioral control in stimulant abusers: the role of prepotent response tendencies. *Drug Alcohol Depend.* 2003;71:143–52.
78. Fillmore MT, Kelly TH, Martin CA. Effects of d-amphetamine in human models of information processing and inhibitory control. *Drug Alcohol Depend.* 2005;77:151–9.
79. Bedard AC, Ickowicz A, Logan GD, Hogg-Johnson S, Schachar R, Tannock R. Selective inhibition in children with attention-deficit hyperactivity disorder off and on stimulant medication. *J Abnorm Child Psychol.* 2003;31(3):315–27.
80. Konrad K, Gunther T, Hanisch C, Herpertz-Dahlmann B. Differential effects of methylphenidate on attentional functions in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2004;43(2):191–8.
81. Fillmore MT, Rush CR, Hays L. Acute effects of cocaine in two models of inhibitory control: implications of non-linear dose effects. *Addiction.* 2006;101:1323–32.
82. Bauer LO. Antisocial personality disorder and cocaine dependence: their effects on behavioral and electroencephalographic measures of time estimation. *Drug Alcohol Depend.* 2001;63:87–95.
83. Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend.* 2002;66:265–73.
84. Lane SD, Cherek DR, Dougherty DM, Moeller FG. Laboratory measurement of adaptive behavior change in humans with a history of substance dependence. *Drug Alcohol Depend.* 1998;51(3):239–52.
85. Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, O’Brian CP, Childress AR. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry.* 2002;51:134–42.
86. 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(21):7839–43.
87. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends Cogn Sci.* 2004;8:170–7.
88. Hester R, Fassbender C, Garavan H. Individual differences in error processing: a review and meta-analysis of three event-related fMRI studies using the GO/NOGO task. *Cerebral Cortex.* 2004;14: 986–94.
89. Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse.* 1993;14:169–77.
90. Volkow ND, Fowler JS, Wang GJ. Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. *J Psychopharmacol.* 1999;13:337–45.
91. Volkow ND, Wang GJ, Ma Y, Fowler JS, Wong C, Ding YS, Hitzemann R, Swanson JM, Kalivas P. Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted

- subjects but not in controls: relevance to addiction. *J Neurosci*. 2005;25:3932–9.
92. Strickland TL, Stein R. Cocaine-induced cerebrovascular impairment: challenges to neuropsychological assessment. *Neuropsychol Rev*. 1995;5(1):69–79.
93. Bolla KI, Cadet JL, London ED. The neuropsychiatry of chronic cocaine abuse. *J Neuropsychiatry Clin Neurosci*. 1998;10(3):280–9.
94. Ardila A, Rosselli M, Strumwasser S. Neuropsychological deficits in chronic cocaine abusers. *Int J Neurosci*. 1991;57(1–2):73–9.
95. Bates ME, Bowden SC, Barry D. Neurocognitive impairment associated with alcohol use disorders: Implications for treatment. *Exp Clin Psychopharmacol*. 2002;10:193–212.
96. Beatty WW, Katzung VM, Moreland VJ, Nixon SJ. Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug Alcohol Depend*. 1995;37(3):247–53.
97. O'Malley S, Adamse M, Heaton RK, Gawin FH. Neuropsychological impairment in chronic cocaine abusers. *Am J Drug Alcohol Abuse*. 1992;18(2):131–44.
98. Jovanovski D, Erb S, Zakzanis KK. Neurocognitive deficits in cocaine users: a quantitative review of the evidence. *J Clin Exp Neuropsychol*. 2005;27(2):189–204.
99. Toomey R, Lyons MJ, Eisen SA, Xian H, Chantarujikapong S, Seidman LJ, Faraone SV, Tsuang MT. A twin study of the neuropsychological consequences of stimulant abuse. *Arch Gen Psychiatry*. 2003;60(3):303–10.
100. Fillmore MT, Rush CR. Polydrug abusers display impaired discrimination-reversal learning in a model of behavioral control. *J Psychopharmacol*. 2006;20:24–32.
101. Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. *J Neurosci*. 2004;24(49):11017–22.
102. Bjork JM, Hommer DW, Grant SJ, Danube C. Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1-/type 2-like traits. *Alcohol*. 2004;34:133–50.
103. Dom G, De Wilde B, Hulstijn W, Van Den Brink W, Sabbe B. Behavioural aspects of impulsivity in alcoholics with and without a cluster-B personality disorder. *Alcohol Alcohol*. 2006;41(4):412–20.
104. Bolla KI, Funderburk FR, Cadet JL. Differential effects of cocaine and cocaine + alcohol on neurocognitive performance. *Neurology*. 2000;54(12):2285–92.
105. Verdejo-Garcia A, Rivas-Perez C, Lopez-Torrecillas F, Perez-Garcia M. Differential impact of severity of drug use on frontal behavioral symptoms. *Addict Behav*. 2006;31(8):1373–82.
106. 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.
107. Perry JL, Carroll ME. The role of impulsive behavior in drug abuse. *Psychopharmacology*. 2008;200:1–26.
108. Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol Biochem Behav*. 2007;86:189–99.
109. Di Sclafani V, Tolou Shams M, Price LJ, Fein G. Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug Alcohol Depend*. 2002;66(2):161–71.

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