

Addiction and Cognition

The brain regions and neural processes that underlie addiction overlap extensively with those that support cognitive functions, including learning, memory, and reasoning. Drug activity in these regions and processes during early stages of abuse foster strong maladaptive associations between drug use and environmental stimuli that may underlie future cravings and drug-seeking behaviors. With continued drug use, cognitive deficits ensue that exacerbate the difficulty of establishing sustained abstinence. The developing brain is particularly susceptible to the effects of drugs of abuse; prenatal, childhood, and adolescent exposures produce long-lasting changes in cognition. Patients with mental illness are at high risk for substance abuse, and the adverse impact on cognition may be particularly deleterious in combination with cognitive problems related to their mental disorders.

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Drug addiction manifests clinically as compulsive drug seeking, drug use, and cravings that can persist and recur even after extended periods of abstinence. From a psychological and neurological perspective, addiction is a disorder of altered cognition. The brain regions and processes that underlie addiction overlap extensively with those that are involved in essential cognitive functions, including learning, memory, attention, reasoning, and impulse control. Drugs alter normal brain structure and function in these regions, producing cognitive shifts that promote continued drug use through maladaptive learning and hinder the acquisition of adaptive behaviors that support abstinence.

In a 2005 review, Steven Hyman stated the current neurological conception of drug abuse concisely: Characterizing addiction as a disease of “pathological learning,” he wrote, “[A]ddiction represents a pathological usurpation of the neural mechanisms of learning and memory that under normal circumstances serve to shape survival behaviors related to the pursuit of rewards and the cues that predict them.”

This article reviews current knowledge on the cognitive effects of drugs and their neurological underpinnings. These effects may be particularly disruptive when individuals are exposed to drugs during brain development, which lasts from the prenatal period through adolescence, and in individuals with mental disorders. An understanding of these issues will help substance abuse clinicians identify and respond to cognitive changes that affect patients’ responses to treatment.

A MULTISTAGE PROCESS

Recent reviews characterize addiction as a two-stage process. In the first stage, the individual's occasional drug taking becomes increasingly chronic and uncontrolled. The neurological source of these symptoms is drug-induced deregulation of the brain's reward system (Feltenstein and See, 2008). Normally, increased dopamine signaling within this system—specifically, in the ventral striatum or nucleus accumbens (NAc)—produces pleasurable feelings that orient organisms to seek and perform life-sustaining conditions and activities, such as locating supportive environments, eating, and having sex. Drugs of abuse hyperactivate this system, triggering abrupt and large increases in NAc dopamine signaling, producing intense sensations that motivate additional drug taking, and promoting the formation of maladaptive drug-stimulus associations (Feltenstein and See, 2008).

Individuals in the second stage of the addictive process present additional clinical features, including withdrawal symptoms during early abstinence, persistent vulnerability to relapse, and alterations in decisionmaking and other cognitive processes. Although modification of the dopaminergic reward system remains important at this stage, it probably is not sufficient to maintain these complex and long-lasting changes. Kalivas and Volkow (2005) summarize evidence implicating drug-induced alterations in signals carried by the neurotransmitter glutamate from the brain area that is primarily associated with judgment—the prefrontal cortex—to the NAc. Le Moal and Koob (2007) emphasize changes in brain stress circuits and negative reinforcement (i.e., effects that motivate drug taking by causing discomfort during abstinence, such as the onset of withdrawal symptoms). Thus, whereas early drug use fosters maladaptive drug-stimulus associations that contribute to drug seeking and use, later stages disrupt cognitive and other processes that are important for successful abstinence.

The full extent of drugs' impacts on cognition is not yet known, but research indicates that addicted individuals have alterations in brain regions including the striatum, prefrontal cortex, amygdala, and hippocampus (Jones and Bonci, 2005; Kalivas and Volkow, 2005; Kelley, 2004; Le Moal and Koob, 2007). These same regions underlie declarative memory—the memories that define an individual, without which it would be difficult to generate and maintain a concept of self (Cahill and McGaugh, 1998; Eichenbaum, 2000; Kelley, 2004; Setlow, 1997). Drugs' capacity to act upon the substrates of declarative memory suggests

that their impact on cognition is potentially extremely far-reaching.

COGNITIVE EFFECTS OF ACUTE DRUG ADMINISTRATION

Clinicians often observe that patients undergoing treatment for addiction become highly vulnerable to relapse when they return to contexts or environments where their addiction developed (Hyman, 2005; See, 2005). Clinical research confirms that cues associated with substance abuse elicit physiological responses and cravings for drugs (Franklin et al., 2007). Laboratory animals, too, develop powerful associations and cue-response behaviors in the presence of drug-related stimuli. For example, animals given a drug in one compartment of a double cage subsequently will gravitate to that compartment more than to the alternative compartment. This phenomenon, known as conditioned place preference, has been demonstrated in studies using nicotine, ethanol, amphetamine, methamphetamine, cocaine, morphine, cannabis, and caffeine (Bardo and Bevins, 2000).

The Formation of Drug-Stimulus Associations

The multistage model of addiction attributes addicted individuals' strong responses to drug cues to a learning process that inculcates powerful drug-stimulus associations (e.g., Robinson and Berridge, 2000). In this view, the individual taking a drug perceives his or her present surroundings as highly significant (salient) and makes exceptionally strong mental connections between features of those surroundings and the intense pleasure of the drug. Subsequently, when he or she re-encounters those features, the powerful associations reassert themselves, consciously or subconsciously, and are experienced as prompts for drug seeking and drug taking. Consistent with this account, exposing addicted individuals to cues that they associate with substance abuse elicits, along with physiological responses and drug cravings, changes in the activity levels of brain regions involved in learning and memory (i.e., striatum, amygdala, orbitofrontal cortex, hippocampus, thalamus, and left insula) (Franklin et al., 2007; Volkow et al., 2006).

The acute effects of amphetamine, nicotine, and cocaine fit straightforwardly into this scenario. Each of these drugs has been shown to acutely enhance learning and/or attention (Del et al., 2007; Kenney and Gould, 2008; Mattay, 1996). For example, the idea that smoking is a cognitive enhancer is well accepted by researchers and the general public. Numerous studies

Drugs act upon brain regions that underlie the memories that define us as individuals.

have confirmed that laboratory animals' cognitive processes improve immediately following administration of nicotine (Kenney and Gould, 2008). Similar findings in early studies with human smokers were not conclusive, because the study participants were smokers who had received nicotine following a period of abstinence. The observed enhancements might have reflected the reversal of withdrawal effects, rather than improvements over their normal cognitive powers. A subsequent review of the literature, however, suggests that acute nicotine enhances reaction time and attention in nicotine-naïve individuals (Swan and Lessov-Schlaggar, 2007). Cocaine produced similar effects in a study of rats that were treated with the drug and then exposed to a sensory stimulus; the animals exhibited enhanced neural activation when later re-exposed to the stimulus (Devonshire, Mayhew, and Overton, 2007).

Although all drugs of abuse foster the learning of strong drug-stimulus associations and cue-induced drug seeking, some appear to have mixed effects on other types of learning and cognition. For example, a clinical study of the acute effects of morphine and oxycodone concluded that these drugs have variable impacts on cognition: Both improved men's recall of prose just slightly, but morphine slightly impaired both sexes' performance on a test of working memory in which they were asked to repeat a set of digits in reverse order (Friswell et al., 2008). In another study, mice were given morphine or saline and trained to run away when a light signaled that a foot shock was impending; although the morphine-treated mice scored higher on the frequency and quickness with which they avoided shocks, the researchers attributed this to increased motor activity rather than enhanced learning (Aguilar, Miñarro, and Simón, 1998).

High doses of alcohol disrupt cognitive processes, while low doses can enhance learning.

In contrast to the effects of opioids on cognition, those of alcohol are clear, though bidirectional: High doses disrupt cognitive processes (Ryback, 1971), while low doses can enhance learning (Gulick and Gould, 2007; Hernández, Valentine, and Powell, 1986).

The Persistence of Drug-Stimulus Associations

Recent research has sought to account for the strikingly long-lasting ability of maladaptive drug-stimulus associations to influence behavior and provoke relapse. Studies have shown that many abused substances can reshape the communication pathways between neurons (synaptic plasticity), which could contribute to both the formation and the persistence of maladaptive drug-stimulus associations.

Cocaine and nicotine can directly induce one form of synaptic plasticity, the strengthening of neural connections via a process known as long-term potentiation (LTP; see Learning in the Mind and Brain on page 8 and Table 1) (Argilli et al., 2008; Kenney and Gould, 2008). Amphetamine can enhance LTP (Delanoy, Tucci, and Gold, 1983). Marijuana activates the endocannabinoid system, resulting in inhibition in some instances and facilitation in others of both LTP and long-term depression (LTD), another form of synaptic plasticity in which connections between neurons become less responsive (Carlson, Wang, and Alger, 2002; Nugent and Kauer, 2008; Sullivan, 2000). Ethanol consistently disrupts LTP while enhancing LTD (Yin et al., 2007). Morphine inhibits LTP of neurons that exhibit inhibitory control of neural activity via the neurotransmitter gamma-aminobutyric acid (GABA) (Nugent and Kauer, 2008). Inhibition of GABA activity could lead to an overall increase in neural activity throughout the brain, which might lead to the formation of stronger associations than would normally occur, including maladaptive drug-context associations.

Strengthening the evidence that drugs foster long-lasting drug-stimulus associations by affecting synaptic plasticity, studies have demonstrated that the same proteins that participate in the sequential biochemical reactions (cell signaling cascades) that control synaptic plasticity (see Figure 1) come into play in drug-seeking behaviors. For example, in one experiment, researchers showed that when rats went to a cage area that they had been trained to associate with cocaine, the levels of proteins associated with learning—extracellular signal-regulated protein kinase (ERK), cyclic AMP response element-binding (CREB), Elk-1, and Fos—increased in

TABLE 1. Drug Effects on Synaptic Plasticity

DRUG	EFFECTS ON PLASTICITY
Amphetamine	LTP
Cocaine	LTP
Ethanol	LTP, LTD
Marijuana	LTP, LTD
Morphine	LTP (of inhibitory synapses)
Nicotine	LTP

LTP, long-term potentiation of synaptic efficiency; LTD, long-term depression of synaptic efficiency.

their NAc (Miller and Marshall, 2005). Moreover, when the rats were treated with a compound that suppresses ERK, they stopped preferring that cage area over one in which they had received saline and showed a decrease in three biochemical participants in LTP (CREB, Elk-1, and Fos) in the NAc.

COGNITIVE DEFICITS IN CHRONIC DRUG ABUSE

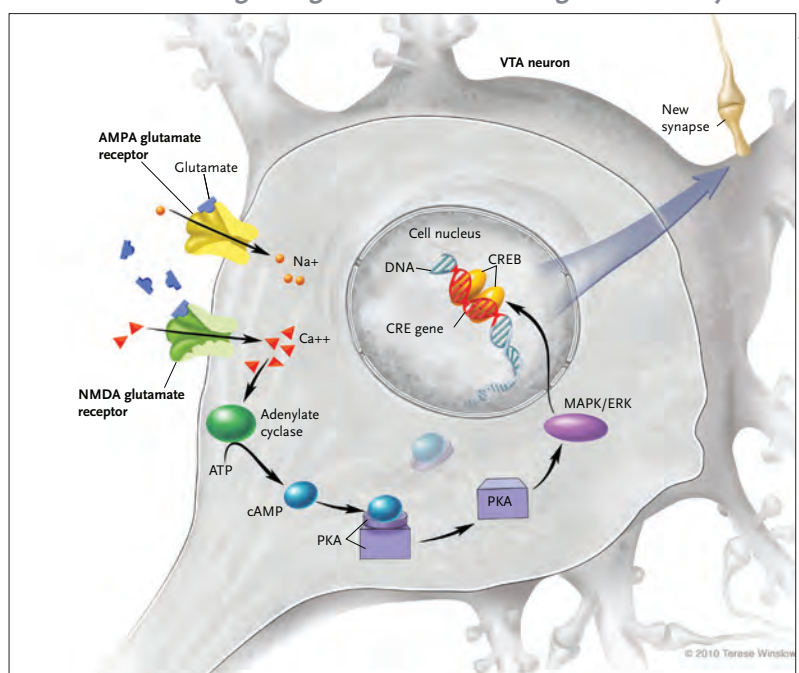
Drug abusers who progress to the second stage of addiction are subject to withdrawal when they initiate abstinence. Many drugs produce cognition-related withdrawal symptoms that may make abstinence more difficult. These include:

- cocaine—deficits in cognitive flexibility (Kelley et al., 2005);
- amphetamine—deficits in attention and impulse control (Dalley et al., 2005);
- opioids—deficits in cognitive flexibility (Lyvers and Yakimoff, 2003);
- alcohol—deficits in working memory and attention (Moriyama et al., 2006);
- cannabis—deficits in cognitive flexibility and attention (Pope, Gruber, and Yurgelun-Todd, 2001); and
- nicotine—deficits in working memory and declarative learning (Kenney and Gould, 2008).

Nicotine provides a familiar example of cognitive changes in withdrawal. In both chronic smokers and animal models of nicotine addiction, cessation of nicotine administration is associated with deficits in working memory, attention, associative learning, and serial addition and subtraction (Bell et al., 1999; Blake and Smith, 1997; Davis et al., 2005; Hughes, Keenan, and Yellin, 1989; Jacobsen et al., 2006; Mendrek et al., 2006; Raybuck and Gould, 2009; Semenova, Stolerman, and Markou, 2007). Moreover, it has been shown that the severity of decreases in cognitive performance during periods of smoking abstinence predicts relapse (Patterson et al., 2010; Rukstalis et al., 2005). Although these deficits usually dissipate with time, a dose of nicotine will rapidly ameliorate them (Davis et al., 2005)—a situation that may contribute to some relapses. Thus, chronic substance abuse can lead to cognitive deficits that are particularly pronounced during early periods of abstinence.

While the cognitive deficits associated with withdrawal from drugs are often temporary, long-term use can also lead to lasting cognitive decline. The nature of deficits varies with the specific drug, the environment,

FIGURE 1. A Cell Signaling Cascade in Learning and Memory



Glutamate binds to α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) receptors in the neuron membrane, opening channels for sodium and calcium to flow into the cell; calcium influx induces adenylate cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP triggers activation, sequentially, of protein kinase A (PKA), mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK), and cAMP response element-binding (CREB). CREB attaches to DNA, increasing DNA production of protein for the construction of new synapses. (For a detailed review of the cellular substrates of learning, see Abel and Lattal, 2001.)

and the user's genetic makeup (see Genes, Drugs, and Cognition on page 11). In general, however, they impair the ability to learn new patterns of thought and behavior that are conducive to successful response to treatment and recovery.

For example, long-term cannabis users have impaired learning, retention, and retrieval of dictated words, and both long-term and short-term users show deficits in time estimation (Solowij et al., 2002), although how long these deficits persist is not yet known. As another example, chronic amphetamine and heroin users show deficits in a range of cognitive skills, including verbal fluency, pattern recognition, planning, and the ability to shift attention from one frame of reference to another (Ornstein et al., 2000). The decisionmaking deficits resembled those observed in individuals with damage to the prefrontal cortex, suggesting that both drugs alter function in that brain area (Rogers et al., 1999).

A pair of recent studies suggests that some methamphetamine-induced cognitive losses may be partially

Cognitive deficits may be particularly pronounced during early periods of abstinence.

LEARNING IN THE MIND AND BRAIN

A mind learns: It captures and stores information and impressions and discovers relationships between them. For the mind to learn, events must occur in the brain. Among the most compelling pieces of evidence for this idea are many cases of individuals who suffered drastic reductions of their ability to learn after incurring brain injuries. The most famous, perhaps, is Henry Molaison, who, after surgical removal of extensive brain tissue at age 27 to control his epilepsy, entirely lost his long-term declarative memory (Penfield and Milner, 1958) so that for the remaining 55 years of his life he could not call to mind anything that happened to him more than a few minutes earlier.

Neuroscience research has correlated learning with the elaboration of neural networks in the brain. Many experiments have established that, as learning takes place, selected neurons increase their levels of activity and form new connections, or strengthen established connections, with networks of other neurons. Moreover, experimental techniques that prevent neuronal activity and networking inhibit learning.

Neuroscience research with animals is elucidating how the brain constructs and maintains the neural networks that support learning. One process identified, long-term potentiation (LTP), has features that parallel key aspects of learning.

- Once we learn to associate two ideas or sensations, the occurrence of one is likely to invoke remembrance of the other. Similarly, in LTP, a neuron that receives strong, or high-frequency, stimulation from another neuron responds by becoming more sensitive to future stimulation from the same source;
- Newly learned material enters our short-term memory and may or may not subsequently become established in our long-term memory. Similarly, LTP has an early phase during which short-term physiological processes support the above-mentioned increase in neuronal sensitivity and a late phase involving more long-lasting physiological processes;
- Animal studies have implicated some of the same sequences of biochemical changes (cell signaling cascades) in LTP and learning. For example, researchers showed that suppressing production of an enzyme (protein kinase A) in the hippocampi of mice prevented LTP and inhibited the animals' ability to retain previously learned information about a maze (Abel et al., 1997).

Although LTP has not been observed in every brain region, it has been demonstrated in the nucleus accumbens, prefrontal cortex, hippocampus, and amygdala—all regions involved in both addiction and learning (Kenney and Gould, 2008; Kombian and Malenka, 1994; Maren, 2005; Otani et al., 2003).

recouped with extended abstinence (Volkow et al., 2001; Wang et al., 2004). Evaluated when abstinent for less than 6 months, chronic methamphetamine abusers scored lower than unexposed controls on tests of motor function, memory for spoken words, and other

neuropsychological tasks. The deficits were associated with a comparative scarcity of dopamine transporters (proteins that regulate dopamine) and reduced cellular activity (metabolism) in the thalamus and NAc. When retested after 12 to 17 months of abstinence, the drug abusers' motor function and verbal memory had risen to levels that approached those of the control group, and the gains correlated with a return toward normal transporter levels in the striatum and metabolic levels in the thalamus; however, other neuropsychological deficits remained, along with depressed metabolism in the NAc.

In another study, abusers of 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy) continued to score relatively poorly in tests of immediate and delayed recall of spoken words even after 2.5 years of abstinence (Thomasius et al., 2006). In a study of polydrug abusers who had stated a primary preference for either cocaine or heroin, deficits in executive function—defined as changes in fluency, working memory, reasoning, response inhibition, cognitive flexibility, and decisionmaking—remained after up to 5 months of abstinence (Verdejo-García, and Pérez-García, 2007).

An important question is whether nicotine's cognitive benefit persists as smoking shifts from sporadic to chronic. In some studies with animals, chronic nicotine administration improved cognitive capacities such as attention, but other studies found that initial improvements waned with chronic treatment (Kenney and Gould, 2008). Furthermore, several recent studies have shown that smoking and a past smoking history are associated with cognitive decline. For example, in one study with middle-aged men and women, smokers' cognitive speed declined nearly twice as much as nonsmokers' over 5 years; in addition, declines in smokers' cognitive flexibility and global cognition occurred at 2.4 times and 1.7 times the respective rates of nonsmokers (Nooyens, van Gelder, and Verschuren, 2008). Recent quitters' scores in these areas were similar to smokers', and ex-smokers performed at levels intermediate between smokers and nonsmokers.

Similarly, in another study, smokers' performance deteriorated more over 10 years than nonsmokers' on tests of verbal memory and speed of visual searching; ex-smokers' visual search speed slowed more than nonsmokers' as well (Richards et al., 2003). Although some early studies suggested that smoking might retard the cognitive decline associated with Alzheimer's disease (van Duijn and Hofman, 1991), followup studies failed

to confirm this, and others correlated smoking quantity and duration with higher risk for Alzheimer's disease (Swan and Lessov-Schlaggar, 2007).

Laboratory studies have demonstrated nicotine-related alterations in neuronal functioning that could underlie cognitive decline that persists even after prolonged abstinence. For example, rats' self-administration of nicotine was associated with a decrease in cell adhesion molecules, a decrease in new neuron production, and an increase in cell death in the hippocampus (Abrous et al., 2002). Such changes could result in long-lasting cognitive changes that contribute to poor decisionmaking and addiction.

DRUGS OF ABUSE AND THE DEVELOPING BRAIN

The human brain continues to develop and consolidate important neural pathways from the prenatal period through adolescence. Throughout these years, the brain is highly malleable, and drug-induced alterations of neural plasticity may deflect the normal course of brain maturation.

Prenatal Exposures

The consequences of prenatal alcohol exposure are well-known: Fetal alcohol spectrum disorders are the leading cause of mental retardation in the United States (Centers for Disease Control and Prevention, 2009). In addition, fetal alcohol exposure increases susceptibility to later substance abuse problems (Yates et al., 1998).

Prenatal exposures to a number of other drugs have significant deleterious effects on cognition and behavior that may not rise to the level of mental retardation. In one study, 5-year-olds whose mothers had used alcohol, cocaine, and/or opiates while pregnant ranked below unexposed controls in language skills, impulse control, and visual attention. There were no significant differences between the two groups of children in intelligence, visual/manual dexterity, or sustained attention; however, both groups placed below the normative means on these measures (Pulsifer et al., 2008). Another study documented memory deficits in 10-year-old children who had been exposed prenatally to alcohol or marijuana (Richardson et al., 2002).

Clinical and laboratory research has implicated prenatal exposure to methamphetamine in both cognitive deficits and altered brain structure. For example, one study correlated shorter attention span and delayed memory with reduced volume in the putamen (-18

percent), globus pallidus (-27 to -30 percent), and hippocampus (-19 to -20 percent) among 15 children aged 3 to 16 years who were prenatally exposed to the stimulant, compared with controls (Chang et al., 2004). The drug-exposed children also exhibited poorer long-term spatial memory and visual/motor integration. Another study documented structural changes in the frontal and parietal cortex of 3- and 4-year-old children who had been exposed prenatally to methamphetamine (Cloak et al., 2009). In laboratory studies, rats that were treated with methamphetamine during pregnancy gave birth to pups that, when they reached adulthood, were slow to learn spatial relationships and exhibited spatial memory impairment (Acuff-Smith et al., 1996; Slamberová et al., 2005).

The effects of prenatal tobacco exposure are particularly concerning because so many expectant mothers smoke—by one estimate, over 10 percent in the United States (Hamilton et al., 2007). *In utero* exposure to tobacco byproducts has been linked to cognitive deficits in laboratory animals and human adolescents (Dwyer, Broide, and Leslie, 2008). Some studies suggest that such exposure can lower general intelligence; for example, one found a 12-point gap in full-scale IQ between exposed and unexposed middle-class adolescents (e.g., Fried, Watkinson, and Gray, 2003). In another study, the odds of having attention deficit hyperactivity disorder (ADHD) were more than three times as great for adolescents whose mothers smoked during pregnancy compared with children of nonsmoking mothers (Pauly and Slotkin, 2008).

Cognitive deficits following prenatal exposure to smoking may reflect structural brain changes. In one study, prenatally exposed adolescent smokers had greater visuospatial memory deficits in conjunction with changes in parahippocampal and hippocampal function compared with adolescent smokers not prenatally exposed (Jacobsen et al., 2006). Brain imaging of adolescent smokers and nonsmokers who were prenatally exposed to smoking has revealed reduced cortical thickness (Toro et al., 2008) and structural alterations in cortical white matter (Jacobsen et al., 2007). Furthermore, in rats, prenatal exposure to nicotine decreased memory-related neural activity in the hippocampus and resulted in deficits in active avoidance learning, with male and female prenatally exposed rats showing significantly fewer correct responses as young adults (Vaglenova et al., 2008). These deficits persisted into later adulthood among the male rats, but not the females.

Cognitive deficits following prenatal exposure to smoking may reflect structural brain changes.

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Among the adverse consequences of prenatal drug exposure is a heightened risk of becoming a drug abuser in later life (Fergusson, Woodward, and Horwood, 1998). This is troubling, as it may lead to a downward spiral that manifests across generations and destroys family structures. Multiple factors could contribute to the increased risk of future substance abuse, including the effects of prenatal drug exposure on cognition. As already reviewed, the risk of developing ADHD is greatly increased in adolescents whose mothers smoked during pregnancy (Pauly and Slotkin, 2008). ADHD is often comorbid with substance abuse (Biederman et al., 2008; Molina and Pelham, 2003), suggesting a link between such changes in cognition and future drug abuse. Further work is needed to understand the mechanisms that underlie the increased risk of drug abuse associated with prenatal exposure.

Adolescent Exposure

Adolescence is a high-risk period for substance abuse. Most addicted smokers first formed the habit during adolescence (Khuder, Dayal, and Mutgi, 1999). Adolescent smoking strongly affects cognition. Adolescent smokers scored worse than age-matched nonsmokers on tests of working memory, verbal comprehension, oral arithmetic, and auditory memory (Fried, Watkinson, and Gray, 2006; Jacobsen et al., 2005). These deficits resolved upon cessation of smoking with the exceptions of working memory and arithmetic performance, which remained at comparatively low levels. In rats, nicotine exposure during adolescence was associated with visuospatial attention deficits, increased impulsivity, and increased sensitivity of medial prefrontal cortical dopamine terminals in adulthood (Counotte et al., 2009). In addition, adolescent rats treated with nicotine had long-lasting changes in the sensitivity of the adenylyl cyclase cell signaling cascade (see Figure 1), a second messenger pathway involved in many processes, including learning and memory (Slotkin et al., 2008). These findings fit well with studies demonstrating that nicotine initially can enhance some cognitive processes, but with continued use adaptation can occur, leading to dissipation of these effects and even deficits (for review, see Kenney and Gould, 2008).

Adolescent smoking can foster cognitive decline indirectly, through the promotion of other disorders. For example, adolescent cigarette use is associated with later episodes of depression (Choi et al., 1997), a malady which in turn is associated with negative effects on cognition

(Thomas and O'Brien, 2008). A laboratory investigation shed light on this relationship: Adult rats that had been exposed to nicotine during their adolescence proved less sensitive than controls to rewarding/appetitive stimuli and more responsive to stress and anxiogenic stimuli (Iñiguez et al., 2009).

Adolescent exposures to other substances of abuse, such as alcohol, cannabis, and MDMA, also cause persistent disruptions of cognition (Brown et al., 2000; O'Shea, McGregor, and Mallet, 2006; Piper and Meyer, 2004; Stiglick and Kalant, 1982). These findings indicate that the adolescent brain, which is still developing, is susceptible to insult from drug use and abuse, and such insult can result in long-lasting changes in affect and cognition.

DRUGS OF ABUSE AND MENTAL ILLNESS

Drug-related cognitive deficits may be particularly detrimental to the well-being of individuals whose cognitive performance is already compromised by a mental disorder. Moreover, individuals who suffer from mental disorders abuse drugs at higher rates than the general population. Substance abuse is almost twice as prevalent among adults with serious psychological distress or major depressive episodes as among age-matched controls (SAMHSA, 2007, p. 85), and it is estimated that over half of U.S. individuals with drug disorders (excluding alcohol) also have mental disorders (Regier et al., 1990). In a 1986 study, smoking rates approximated 30 percent in population-based controls, 47 percent in patients with anxiety disorder or major depressive disorder, 78 percent in patients with mania, and 88 percent in patients with schizophrenia (Hughes et al., 1986).

The case of smoking and schizophrenia provides one example of a mental disorder that features cognitive deficits in combination with abuse of a drug that causes cognitive decline. As with many comorbidities, effective treatment will likely require untangling the reasons why the two conditions so frequently co-occur:

- Some evidence suggests that patients with schizophrenia smoke to self-medicate. For example, smoking reverses schizophrenic patients' deficits in the brain's ability to adapt its responses to stimuli (sensory gating), which could reduce the capacity to filter information, and might account for some of the cognitive disruption seen in the mental disorder. Researchers have traced this feature of schizophrenia to a variant of the gene for the $\alpha 7$ nicotinic acetylcholinergic receptor subunit (Leonard et al., 2001). Consistent with this viewpoint

is an observation that patients smoke less when given the antipsychotic clozapine, which independently alleviates this deficit, than when given haloperidol, which does not (McEvoy, Freudenreich, and Wilson, 1999).

- It has also been proposed that patients with schizophrenia smoke to alleviate side effects of antipsychotic medication (Goff, Henderson, and Amico, 1992). An observation that supports this idea is that patients with schizophrenia smoke more after receiving the antipsychotic haloperidol than when unmedicated (McEvoy et al., 1995).
- Another suggested explanation for the link between smoking and schizophrenia is that smoking itself may precipitate schizophrenia in people predisposed to develop the disease. Among schizophrenics, smokers have an earlier onset of illness, require hospital admissions more frequently, and receive higher doses of antipsychotic medications (Goff, Henderson, and Amico, 1992; Kelly and McCreddie, 1999; Ziedonis et al., 1994).

Another cognitive disorder that is strongly associated with smoking is ADHD. Interestingly, the cognitive symptoms associated with ADHD are similar to those displayed during nicotine withdrawal, and both have been attributed to alterations in the acetylcholinergic system (Beane and Marrocco, 2004; Kenney and Gould, 2008). The high prevalence of smoking among individuals with ADHD (Lambert and Hartsough, 1998; Pomerleau et al., 2003) may be an attempt to self-medicate, because acute nicotine use can reverse some ADHD attentional deficits (Conners et al., 1996). The desire to avoid withdrawal may be a particularly strong motivation for continued smoking in this population, as individuals with ADHD suffer more severe withdrawal symptoms than age-matched controls without the disorder (Pomerleau et al., 2003), and increases in ADHD symptoms following smoking cessation are associated with a greater risk of relapse (Rukstalis et al., 2005). As noted above, however, continued smoking in itself can lead to cognitive decline (Nooyens, van Gelder, and Verschuren, 2008; Richards et al., 2003), and hence might exacerbate ADHD-related symptoms.

Along with nicotine, ADHD is also associated with abuse of stimulants, such as amphetamine and cocaine, and psychoactive drugs, such as cannabis (Elkins, McGue, and Iacono, 2007; Galéra et al., 2008; Tang et al., 2007). Such abuse may also represent attempts at self-medication, as stimulants are used to treat ADHD symp-

GENES, DRUGS, AND COGNITION

An individual's genetic makeup can influence the degree to which a drug of abuse alters his or her cognitive processes. For instance, an individual's cognitive response to acute amphetamine depends in part on which of the alternative forms of the *catechol-O-methyltransferase (COMT)* gene he or she has inherited.

This gene encodes a protein that metabolizes dopamine and norepinephrine, among other molecules. A person inherits two copies of the gene, one from each parent, and each copy has either a valine or a methionine DNA triplet at codon 158: thus, a person may have two valine (Val/Val), two methionine (Met/Met), or a mixed pair (Val/Met or Met/Val) of codons at this location. Administration of acute amphetamine to individuals with the Val/Val pairing improved their performance on the Wisconsin Card Sorting Task (a test of cognitive flexibility that activates the dorsolateral prefrontal cortex) and increased efficiency in their prefrontal cortical function, as measured by increased regional cerebral blood flow in the inferior frontal lobe (Mattay et al., 2003). However, acute amphetamine did not produce those advantages in individuals with either the Val/Met or Met/Met pairing. Interestingly, the Val/Val pairing is also associated with increased impulsivity, a trait associated with addiction (Boettiger et al., 2007).

Furthermore, smokers with the Val/Val pairing were more sensitive to the disruptive effects of nicotine withdrawal on working memory and exhibited a greater cognitive response to tobacco (Loughead et al., 2009). These results are important not only because they demonstrate a link between the effects of drugs of abuse on cognition and behavioral traits associated with addiction, but also because they provide examples of how genotype contributes to the addictive phenotype.

toms (Dopheide and Pliszka, 2009; Kollins, 2008) such as deficits in attention and working memory (Beane and Marrocco, 2004). Some of the distress of ADHD may reflect a reduction in dopaminergic function (Volkow et al., 2009), which might be partially compensated by drugs of abuse (Feltenstein and See, 2008).

CLINICAL IMPLICATIONS

The literature reviewed here highlights the importance of considering past and present cognitive function when treating patients for addiction, as drug-related cognitive changes may bias patients toward responses and actions that contribute to the cycle of addiction. Clinicians face the challenge of helping patients master adaptive strategies to overcome the strong associations that contribute to relapse when patients return to environments associated with their prior substance use. In addition, cognitive deficits may hinder patients' ability to benefit from counseling, and more sessions and/or reminders may be necessary to aid these patients in incorporating

The cognitive symptoms associated with attention deficit hyperactivity disorder are similar to those displayed during nicotine withdrawal.

abstinence-sustaining strategies into their daily routines.

Research into the changes in cognition that accompany addiction and the neural substrates of learning and addiction is still in its infancy but has potential to reshape views on addiction. For example, a recent discovery that has generated excitement in the addiction field is that smokers who suffered damage to the insula often lost their desire to smoke (Naqvi et al., 2007). The authors of this finding proposed that the insula is involved in the conscious urge to smoke and that therapies that modulate insula function may facilitate smoking cessation. It may also be that damage to the insula will have a similar effect on the desire to use other drugs of abuse (for a review see Goldstein et al., 2009).

A better understanding of how substances of abuse change cognitive processes is needed to develop new therapeutic agents to treat addiction and ameliorate cognitive deficits. This is a complex issue, however, as different drugs of abuse appear to alter different cognitive processes and cell signaling pathways. Even among users of the same drug, cognitive impacts will differ depending on variations in environmental factors and genetics. Understanding the influence of an individual's

genetic background on the manifestation of symptoms is a critical area for future research, holding the promise of informing more effective treatments that can be tailored to the individual's genotype. Finally, understanding how prenatal exposure to drugs of abuse changes neural development should be a high priority, as prenatal exposure increases the new generation's susceptibility to addiction and other problems.

ACKNOWLEDGMENTS

The author would like to thank Dr. Sheree Logue and members of the Gould Laboratory for critically reading an earlier version of this review and also to acknowledge support by grants from the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the National Cancer Institute (AA015515, DA017949, DA024787, and P50 CA143187) for some of the studies reviewed.

CORRESPONDENCE

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