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Are adolescents more vulnerable to drug addiction than adults? Evidence from animal models

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Abstract

Background and rationale—Epidemiological evidence suggests that people who begin experimenting with drugs of abuse during early adolescence are more likely to develop substance use disorders (SUDs), but this correlation does not guarantee causation. Animal models, in which age of onset can be tightly controlled, offer a platform for testing causality. Many animal models address drug effects that might promote or discourage drug intake and drug-induced neuroplasticity.

Methods—We have reviewed the preclinical literature to investigate whether adolescent rodents are differentially sensitive to rewarding, reinforcing, aversive, locomotor, and withdrawal-induced effects of drugs of abuse.

Results and conclusions—The rodent model literature consistently suggests that the balance of rewarding and aversive effects of drugs of abuse is tipped toward reward in adolescence. However, increased reward does not consistently lead to increased voluntary intake: age effects on voluntary intake are drug and method specific. On the other hand, adolescents are consistently less sensitive to withdrawal effects, which could protect against compulsive drug seeking. Studies examining neuronal function have revealed several age-related effects but have yet to link these effects to vulnerability to SUDs. Taken together, the findings suggest factors which may promote recreational drug use in adolescents, but evidence relating to pathological drug-seeking behavior is lacking. A call is made for future studies to address this gap using behavioral models of pathological drug seeking and for neurobiologic studies to more directly link age effects to SUD vulnerability.

Keywords

Addiction; Alcohol; Cocaine; Amphetamine; Nicotine; Cannabinoids

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Introduction

Drugs such as cocaine, amphetamine, nicotine, alcohol, and marijuana are commonly used for their mood- and mind-altering properties. These substances also have the potential to be addictive. In some people, regular use leads to “addiction” or “dependence,” i.e., compulsive and repetitive drug-seeking behavior despite negative health and social consequences. However, this type of behavior does not occur in all users (see Fig. 1). Many people who experiment with drugs do not find the effects rewarding and avoid them in the future. Some people enjoy the effects of the drugs and use them recreationally without ever becoming dependent. For others, however, the drugs gain powerful control over their lives and may replace all other healthy pursuits (see Fig. 1). The majority of people who self-administer drugs of abuse begin during adolescence. Epidemiological studies have shown that earlier onset of drug intake is associated with greater likelihood of development of substance use problems. However, there is debate about whether early onset uniquely affects brain development in such a way as to promote pathological behavior or whether the same genetic and environmental factors that make an individual likely to develop drug problems also make them likely to initiate early. This review summarizes results from animal models in which the effect of age of onset has been examined.

The terms “addiction,” “drug abuse,” and “drug dependence” are used interchangeably in the vernacular and have varying definitions in psychological, sociological, and neuroscience literature. For the sake of clarity, we will refer to the two substance use disorders (SUDs), drug dependence and drug abuse, as they are defined by the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV 1994).

For a diagnosis of drug abuse, a patient must present at least one of the following four characteristics:

1. Recurrent substance use resulting in the failure to fulfill major role obligations at work, school, or home
2. Recurrent substance use in situations in which it is physically hazardous
3. Recurrent substance-related legal problems
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

For a diagnosis of drug dependence, a patient must present three of the following seven characteristics:

1. Tolerance
2. Withdrawal
3. The substance is taken in larger amounts or over a longer period than was intended
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of substance use
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

Two of the criteria for drug dependence, withdrawal and tolerance, relate to physiological phenomena that ensue from repeated drug taking and are relatively easy to measure in animal models. New behavioral methods are approaching success at modeling increased intake, intake despite negative consequences, and the choice between drug intake and other activities, as described below.

The DSM-IV criteria provide a "snapshot" that clinicians can use when a patient requires diagnosis or treatment. However, drug dependence is actually a progressive disease, with several defined stages that often overlap with adolescence (Kreek et al. 2005; see Figs. 1 and 2). Drug dependence necessarily begins as experimental drug use; no person can become dependent without first taking a drug. Most people try drugs (at least alcohol or tobacco) at some point in their lives, typically experimenting during the late teenage years and early 20s (Chen and Kandel 1995). Some users repeat drug use under recreational circumstances. Recreational drug use can vary widely but is defined by the fact that the user has control over it. Recreational users seek drugs for their rewarding properties and not out of compulsion (Kalivas and Volkow 2005). Drug abuse and dependence begin to emerge when use becomes compulsive. The likelihood of progression from experimentation to recreational use to dependence varies by drug. Figure 1 provides a visual interpretation of this point by depicting the percentage of the population of the USA over age 12 that has ever taken a particular drug, uses regularly, or is dependent. Although the percentage that develops dependence varies by drug and is likely influenced by cultural and legal factors, the dependent population represents a small subset of those who have experimented with a drug. A key research question, therefore, is why do some drug users develop SUDs, while others can remain purely recreational?

Epidemiological studies have provided insight into some factors that explain the difference between recreational users and those with SUD. One frequently observed correlation is that people who begin use at a young age are more likely to develop SUDs (Robins and Przybeck 1985; Meyer and Neale 1992; Lewinsohn et al. 1999; Prescott and Kendler 1999; DeWit et al. 2000; Lynskey et al. 2003; Brown et al. 2004; Patton et al. 2004) and tend to progress faster from experimentation to problem use (Chen and Kandel 1995; Chen et al. 1997). This correlation is the focus of the present review. Other contributing factors include family history of SUDs (Hoffmann and Su 1998; Hill et al. 2000) and psychopathology such as depression, anxiety, attention deficit disorder, schizophrenia, and conduct disorder (Deykin et al. 1987; Russell et al. 1994; Burke et al. 1994; Abraham and Fava 1999; Compton et al. 2000; Shaffer and Eber 2002; Costello et al. 2003). All of these factors are *associated* with increased risk of development of SUDs, but causality is difficult to address in human populations. In this review, we will examine attempts in animal models to address the question of whether drug taking at a young age is *causal* or merely coincidental in SUD development.

It is crucial at this point to define what we mean by "young." Experimentation with alcohol, tobacco, and marijuana typically begins during the teenage years (SAMHSA 2008). Use of alcohol peaks around age 18–20 and declines into adulthood (Chen and Kandel 1995). Marijuana and tobacco use peaks slightly later, between ages 19 and 22 (Chen and Kandel 1995). Cocaine use peaks in the early to mid-20s and also declines into adulthood (Chen and Kandel 1995). The typical age-related pattern of drug use involves experimentation in the late teens and early 20s, so those who experiment before these typical times (alcohol and cigarettes in late childhood or the early teens or illegal drugs in the teens) are the most at risk. While many studies use an age of onset before 15 years as the cutoff for "early onset," there is, in general, an inverse correlation: younger users are more likely to develop SUDs.

While the inverse correlation between age of onset and SUD liability is well established in humans, it does not tell us whether early use is causal. Epidemiological studies to test causality require twin or longitudinal studies which are difficult and rare. Two twin studies have resulted in conflicting results, albeit with different substances. One large study examining the risk for alcohol abuse and dependence reported that age of onset was correlated with but not causal in development of alcohol use disorders (Prescott and Kendler 1999). In contrast, a smaller study of twins who were discordant for early-onset marijuana use reported that age of onset was causal in development of later drug use and abuse problems (Lynskey et al. 2003). Thus, there is sparse evidence and lingering debate within the epidemiological literature regarding the causality of early-onset drug use as it relates to later drug problems. Human studies show that family history and psychopathology both increase the likelihood of early initiation (Tarter et al. 1999; Franken and Hendriks 2000; McGue et al. 2001a, b). Do these biological and environmental effects, therefore, operate through early initiation to increase vulnerability to SUDs? Or would users with a family history and/or psychopathology develop SUDs no matter when they initiate? These questions are difficult to address in human studies. To fully address the causality of early drug exposure on later SUD, animal models are necessary.

Animal models have the distinct advantage of experimental control. Experimenters can randomly assign the age of initial exposure, as well as the drug, dose, duration, and timing of exposure, whereas, in human studies, these conditions are determined by the user. For this reason, animal models have provided much valuable information. However, one drawback to animal use is that no model completely recapitulates the stages in development of SUD. For this reason, we must integrate results from multiple behavioral and neurobiological models to achieve a full understanding.

Rodent behavioral models of substance use disorders

Rodent behavioral tasks model basic processes that are components of SUD pathology but cannot completely mimic the disease. Multiple models have been used which vary in validity and relevance to the human condition and are summarized below and in Fig. 2.

Conditioned place preference—Conditioned place preference (CPP) is designed to assess whether a drug is rewarding. The animal is trained to associate a place with the rewarding effects of experimenter-injected drug-induced sensations. If the animal later freely approaches the drug-associated place, then the drug is deemed rewarding (Carr et al. 1989; Bardo and Bevins 2000). Rewarding drugs, it is assumed, are more likely to be sought than nonrewarding drugs. This test is useful in measuring the level and persistence of drug-induced reward. It is not a useful model of pathological drug seeking or taking. This test is also highly dose sensitive: drugs of abuse are typically rewarding at low to moderate doses and aversive at high doses.

Conditioned place and taste aversion—These tests are designed to assess aversive effects of drugs of abuse. It is assumed that aversive effects discourage intake. In these tasks, the animals are trained to associate a place or an otherwise palatable flavor with the sensations ensuing from an experimenter-injected drug (Welzl et al. 2001). Subsequent avoidance of the place or flavor indicates aversive effects. These tests measure the use-limiting effects of drugs of abuse but do not model pathological drug seeking or taking.

Withdrawal—Withdrawal is a constellation of affective and physiological changes that occurs after cessation of intake of some drugs of abuse. Symptoms vary based on the drug consumed, duration, and extent of exposure and generally reflect the reversal of initial drug effects. Many of these behaviors are easily quantified in animal models. For example,

ethanol withdrawal is marked by signs of autonomic arousal and behavioral activation such as piloerection, locomotor activation, tremor, and seizures (Majchrowicz 1975). Withdrawal from opiates elicits both behavioral and autonomic activation as indicated by ptosis, teeth chatter, lacrimation, wet dog shakes, and jumping (Rasmussen et al. 1990). Withdrawal from nicotine includes autonomic and behavioral signs such as body shakes, tremors, writhing, escape attempts, chewing, gasping, ptosis, teeth chattering, and yawning (O'Dell et al. 2007b). All of these signs are analogous to effects in humans (DSM-IV 1994). For psychostimulants such as cocaine and amphetamine, physiological withdrawal signs such as these are rarely observed (DSM-IV 1994). Withdrawal from the psychostimulants and most other drugs of abuse elicits a generalized "negative motivational state" characterized by elevated reward threshold which can be assessed using intracranial self-stimulation (O'Dell et al. 2007b). Withdrawal also elicits an anxiety-like state which can be assessed using multiple models such as the social interaction test, elevated plus maze, light–dark task, and others (see below).

Locomotor behaviors—Most abused drugs stimulate locomotor behavior through activation of the dopaminergic circuits that contribute to their reinforcing effects (Wise 1987; Di Chiara 1995). Cocaine and amphetamine typically increase motor activity in two ways. At lower doses, ambulatory activity is increased, which is most often measured as an increase in matrix crossings or distance traveled. At higher doses, locomotion falls and stereotypic behavior can emerge, which is manifested as an increase in sniffing, grooming, head bobbing, or other repetitive behaviors and a consequent decrease in distance traveled. Ethanol, in humans, tends to be activating at low doses (which may result from reduced inhibitions) and sedating at high doses (DSM-IV 1994). In rats, ethanol has been reported to either increase or decrease locomotion, but dose effects do not consistently parallel the human pattern (see below). Similarly, nicotine can either increase or decrease locomotion in rodents (see below). Opiates can also cause locomotor activation (Buxbaum et al. 1973; Pert and Sivit 1977; Kalivas et al. 1983). Mu opioid agonists cause locomotor stimulation in both mice and rats, and repeated treatment causes sensitization (Rethy et al. 1971; Babbini and Davis 1972; Stinus et al. 1980; Kalivas and Stewart 1991; Gaiardi et al. 1991). In summary, acute motor responses are one indicator of drug sensitivity but are highly variable.

Repeated exposure to any of these drugs can lead to a phenomenon called sensitization, in which the ambulatory or stereotypic response to a repeated low dose is augmented (Shuster et al. 1975a, b, 1977, 1982; Aizenstein et al. 1990; Segal and Kuczenski 1992a, b). Sensitization is a manifestation of neuroplastic changes in response to repeated exposure, and some researchers have hypothesized that it is a behavioral correlate of increased drug craving and development of dependence (Robinson and Berridge 1993, 2000, 2001, 2008), although others debate this assertion (Di Chiara 1995). Clearly, sensitization represents a lasting neuroplastic change that is easily measured. Its relevance to drug dependence is still debated.

Self-administration—Since humans who become drug addicts voluntarily consume drugs, it is important to examine animal models in which drugs are voluntarily administered (or "self-administered") by the animal. For drugs such as cocaine and nicotine, self-administration (SA) in rodents is achieved via intravenous administration through indwelling jugular catheters (since rodents will not reliably snort or smoke these compounds). Admittedly, while most adolescent humans do not use the intravenous route to administer cocaine and nicotine, they do utilize routes which result in rapid absorption of the drugs into the blood (insufflation of cocaine, smoking of crack cocaine and nicotine). Ethanol presents a much simpler model because oral ingestion is easily performed in rodents, as long as taste, caloric intake, and fluid balance are properly controlled. Both oral

and intravenous approaches have been used to assess the age dependence of voluntary intake in animal models.

Animals that acquire drug-seeking behavior more quickly or perform it more frequently are thought to resemble human drug addicts. However, drug taking, even when it is acquired quickly, is not equivalent to drug dependence. Experimental animals will also work to obtain food and other environmental conditions in the absence of any abuse liability. Dependence-like behaviors require more complex testing, and there are several more sophisticated operant conditioning methods currently in use that provide better models of SUDs. One such example is progressive ratio responding, in which each successive infusion requires more lever presses than the previous one. This schedule is designed to assess motivation to seek the drug (Hodos 1961; Roberts et al. 1989; Depoortere et al. 1993). Extinction and reinstatement paradigms are used to model relapse (de Wit and Stewart 1981; Shaham et al. 2003). Timeout and punished responding are used to model compulsive use (Vanderschuren and Everitt 2004; Deroche-Gamonet et al. 2004). Extended access or long-access (LgA) training schedules are used to model high-level or binge use (Knackstedt and Kalivas 2007; O'Dell et al. 2007a; George et al. 2008; Mantsch et al. 2008). In a comprehensive self-administration model, Deroche-Gamonet et al. (2004) combined several of these measures and observed that a small percentage of self-administering rats exhibited multiple dependence-like behaviors, similar to the results obtained in the human population shown in Fig. 1. These models are just beginning to appear in studies comparing adolescents and adults.

Ranking the behavioral models—The relevance of each of these rodent models to human SUD can be debated. In the analysis that follows, we assign greater weight to methods which come closest to modeling human SUD and less weight to models which are not clearly linked to pathological drug intake. Therefore, studies using the more complex methods of self-administration (progressive ratio, extinction, reinstatement, punishment, LgA, etc.) are likely to be the most informative regarding vulnerability to SUD. However, these are the newest techniques, are the most difficult to employ in developmental studies, and consequently are the least examined in adolescent vs. adult rodents. Next, we assign approximately equal weight to studies examining the reinforcing, rewarding, aversive, and withdrawal-related effects of these drugs (simple self-administration, conditioned place preference, conditioned taste/place aversion, and withdrawal measures, respectively). All of these measures are related to the phenomena which promote or discourage drug taking and are therefore useful indirect measures of propensity for drug intake. We rank the locomotor effects of drugs of abuse as less compelling in their validity. Acute locomotor effects are useful indicators of drug sensitivity, and sensitization is widely used as a surrogate for reinforcement. However, locomotion and reinforcement involve overlapping but nonidentical processes (Di Chiara 1995; Robinson and Berridge 2008; Vezina and Leyton 2009).

In addition to varying relevance to human SUD, these models vary in the phase of development of SUD that they model. Self-administration models both early and late phases of the disease. CPP, conditioned place aversion (CPA), conditioned taste aversion (CTA), and acute locomotor effects model early drug intake, sensitization models repeated intake, and withdrawal model long-term use and attempted abstinence. See Fig. 2.

In this review, we will summarize results from animal models in which the effects of age of onset of drug exposure have been examined in adolescent vs. adult rodents. This comparison is crucial: many studies have examined effects in adolescents only or in adults which were preexposed as adolescents, but such studies do not test for age specificity of the findings. The review focuses on nicotine, ethanol, marijuana, and psychostimulants, as there is a

significant literature comparing the effects of these drugs in adolescents and adults. Unfortunately, there are only a few studies which examine narcotics in adolescents (for example, see Zhang et al. 2008). The outline of the review will follow the path from initial use through addiction. We will begin by examining the effects of a single or a few drug administrations in which the rewarding, aversive, and locomotor effects have been examined. We will then discuss the effects of long-term voluntary intake via oral and intravenous self-administration. Finally, we will discuss evidence from withdrawal studies which model the likely consequences of attempts to quit.

In general, the results obtained from rodent models suggest that:

1. Adolescents find some addictive drugs more rewarding than adults
2. Adolescent rodents are consistently less likely to demonstrate aversive effects of drugs of abuse
3. Adolescent rodents may self-administer higher doses of some drugs of abuse under some conditions
4. Adolescent rodents consistently experience less severe withdrawal effects

These conclusions, for which we will provide evidence below, suggest that the developmental stage of adolescence itself could increase early drug taking because addictive drugs are on balance more rewarding and less aversive. However, these studies do not provide any support for the possibility that progression to compulsive use is more likely when drug use begins in adolescence: the critical studies have not been done.

The review will begin with a description of adolescent development in rodents as compared to humans. We will then examine results from studies in which each model has been used to compare adolescent and adult exposure.

Adolescent rodents as models of adolescent humans

We have focused on rodent models of addiction-related behavior because of the extensive data published using these models and the relative simplicity of comparing adolescent and adult rodents. While primate models would be very informative, we found only one study directly comparing drug effects in adolescent vs. adult primates (Schwandt et al. 2007). Based on data that are reviewed extensively elsewhere (Spear 2000), we will consider the age range of 28–42 days to be “adolescence” in rodents. By hormonal, physical, and social maturation criteria, this phase of development corresponds to age 12–18 years in humans (Spear 2000). It is critical to mention that animals are not uniform through this time period. In fact, some behavioral measures discussed below differ markedly between 28- and 42-day-old rodents, much as addiction vulnerability differs markedly between 12- and 18-year-old humans.

Growing evidence suggests that adolescent humans and rodents experience many similar structural and functional changes in the brain as they progress to adulthood. For example, forebrain dopamine innervation is still maturing in both humans (Seeman et al. 1987) and rodents. Dopamine D1 and D2 receptor levels reach a peak and then decline over adolescence (Gelbard et al. 1989; Teicher et al. 1995; Andersen and Teicher 2000). In addition, connections between the amygdala and prefrontal cortex mature during this phase, as demonstrated by microscopy studies in rodents (Cunningham et al. 2002, 2008) and functional magnetic resonance imaging studies in humans (Ernst et al. 2005; Eshel et al. 2007). Thus, brain development during adolescence is likely similar in many ways between humans and rodents.

Early drug exposure

As shown in Fig. 2, the necessary first step toward development of drug dependence is drug intake. The quality of the first drug experience is crucial in determining future intake: for most drugs, people who enjoy their initial experiences are more likely to repeat drug intake (Haertzen et al. 1983). Drugs of abuse exert both rewarding and aversive effects (Wise et al. 1976), and the overall balance between these experiences during early drug use determines whether an individual will repeat drug taking in the future. In rodents, as described above, CPP, CPA, and CTA are used to assess initial reward and aversion and have provided valuable insight into the age dependence of such effects.

Rewarding effects

Some have speculated that elevated drug use in adolescence occurs because younger users find drugs more rewarding (Vastola et al. 2002; Belluzzi et al. 2004; Badanich et al. 2006; O'Dell 2009). There is some evidence that younger people and rodents derive greater reward from natural substances (Vaidya et al. 2004), which could generalize to addictive substances. If so, then younger users would likely take a drug more frequently or at higher doses, which could explain the faster progression to dependence seen in adolescents. Evidence to address this crucial question is mixed but indicates that adolescents are more sensitive to the rewarding effects of at least some drugs.

Nicotine is consistently more rewarding in adolescents (Vastola et al. 2002; Belluzzi et al. 2004; Torrella et al. 2004; Shram et al. 2006; Kota et al. 2007; Brielmaier et al. 2007; Torres et al. 2008). One study has shown that *ethanol* is more rewarding in adolescents (Philpot et al. 2003). Studies of psychostimulant reward (*cocaine*, *amphetamine*, *methamphetamine*) are more mixed but tend to indicate greater reward sensitivity in adolescents, particularly at lower doses (Badanich et al. 2006; Brenhouse and Andersen 2008; Brenhouse et al. 2008; Zakharova et al. 2008a, [b]; but see Aberg et al. 2007; Adriani and Laviola 2003; Balda et al. 2006; Campbell et al. 2000; Schramm-Sapyta et al. 2004; Torres et al. 2008). Tetrahydrocannabinol (THC) does not elicit strong conditioned place preferences in rodents. See Table 1. Overall, conditioned place preference studies suggest that adolescents are likely to find many drugs of abuse more rewarding, especially at threshold doses. More systematic dose–effect comparisons are needed in the literature.

Aversive effects

There is a clear consensus in the literature that adolescent rodents are less susceptible to aversive effects of every abused drug that has been tested. This is true for *nicotine* (Wilmouth and Spear 2004; Shram et al. 2006), *ethanol* (Philpot et al. 2003; and Schramm-Sapyta et al., unpublished observations), *THC* (Schramm-Sapyta et al. 2007; Quinn et al. 2008), *amphetamine* (Infurna and Spear 1979), and *cocaine* (Schramm-Sapyta et al. 2006); see Table 1. In fact, conditioned taste aversion for a nonaddictive substance, *lithium chloride*, is also reduced in adolescent rats (Schramm-Sapyta et al. 2006), suggesting that insensitivity to aversive effects may be a generalized feature of adolescence. In addition to these direct tests of aversive effects, other potentially use-limiting effects of many drugs of abuse are reduced in adolescents compared to adults. For example, *nicotine* is anxiolytic in adolescent male rats but anxiogenic in adults (Elliott et al. 2004). Adolescent rats are less sensitive to *ethanol's* social inhibitory effects (Varlinskaya and Spear 2004b), hangover-induced anxiety (Doremus et al. 2003; Varlinskaya and Spear 2004a), and sedative effects (Little et al. 1996; Swartzwelder et al. 1998). The anxiogenic and sedative effects of *THC* are also reduced in adolescence (Schramm-Sapyta et al. 2007). Overall, either the severity of aversive effects or the ability to learn from an aversive experience is globally reduced in

adolescence, which may facilitate higher or more frequent drug intake in adolescents compared to adults.

Locomotor effects

As described above, the locomotor effects of drugs of abuse can be used to examine age-related effects on drug sensitivity and drug-induced neuroplasticity. A large number of published studies have examined these phenomena, which we will now summarize.

Acute locomotion—The acute locomotor effects of drugs of abuse are highly variable and age, drug, and laboratory specific. *Nicotine* can either increase or decrease locomotion. There is debate in the literature as to what determines the direction of nicotine's locomotor effects (Jerome and Sanberg 1987), so it is not surprising that the role of age is also debated. Two studies observed increased locomotion in adolescents but decreased locomotion in adults (Vastola et al. 2002; Cao et al. 2007a). Another study observed decreased locomotion in adults and midadolescents (45 days old) but no effect in young adolescents (28 days old; Belluzzi et al. 2004). Two studies observed decreased locomotion in both ages, with greater effects in adolescents (Lopez et al. 2003; Rezvani and Levin 2004). Four other studies have observed increased locomotion in both ages to an equal extent (Faraday et al. 2003; Schochet et al. 2004; Collins et al. 2004; Cruz et al. 2005). One study reported greater acute locomotion in adolescents (Collins and Izenwasser 2004). These conflicting results were obtained despite a similar range of nicotine doses across the studies. Reports for *ethanol* are similarly inconclusive despite similar doses examined across studies. One study reported greater motor reduction in adult mice (Lopez et al. 2003), while another study reported equal locomotor reduction in the two ages (Rezvani and Levin 2004). Another study reported locomotor activation in both ages, with a greater effect on adolescents (Stevenson et al. 2008). In primates, ethanol's ataxic effects decrease with age, while impairment of jumping ability and motor stimulation increased with age across adolescence (Schwandt et al. 2007). *Amphetamine* and *cocaine* both increase locomotion. Adolescents are consistently hyporesponsive (in terms of both ambulatory and stereotypic activity) to *amphetamine* and *methamphetamine* compared to adults (Lanier and Isaacson 1977; Bolanos et al. 1998; Laviola et al. 1999; Zombeck et al. 2009). However, in response to *cocaine*, studies comparing rats in the third or fourth week of life (preadolescence to early adolescence) to rats in the fifth or sixth week of life (midadolescence to late adolescence) generally report greater ambulation and stereotypy in the early adolescents (Spear and Brick 1979; Snyder et al. 1998; Caster et al. 2005; Parylak et al. 2008). Most investigators then observe no change from late adolescence to adulthood (Laviola et al. 1995; Maldonado and Kirstein 2005; Caster et al. 2005; Parylak et al. 2008), while others have observed a slight trend toward reduced ambulation and stereotypy in adolescents compared to adults (Laviola et al. 1995; Frantz et al. 2007), particularly in females (Laviola et al. 1995). *Morphine* stimulates greater locomotor activation in adolescents than adults (Spear et al. 1982). Overall, there is no consensus in the literature regarding the relationship of age to acute locomotor effects of drugs of abuse.

Sensitization—Many reports have examined the effect of age on locomotor sensitization to psychostimulants. Sensitization clearly changes developmentally. It is absent in the early neonatal period and emerges as animals mature (Kolta et al. 1990; McDougall et al. 1994; Ujike et al. 1995). For cocaine, amphetamine, methamphetamine, and phencyclidine, detectable levels of sensitization become apparent during late neonatal development and early adolescence, between the third and fourth postnatal week (Tirelli et al. 2003). Once sensitization is detectable, there is debate about whether it changes in adolescence.

For *nicotine*, some experimenters have observed reduced sensitization in adolescents (Schochet et al. 2004; Collins et al. 2004; Collins and Izenwasser 2004; Cruz et al. 2005); some have observed greater sensitization in adolescents (Belluzzi et al. 2004; Adriani et al. 2006); and others have observed no age effect (Faraday et al. 2003), particularly in females (Collins et al. 2004; Collins and Izenwasser 2004). Therefore, the literature indicates that nicotine is not globally more sensitizing in adolescents than adults. One study has examined sensitization in response to *ethanol* and found that adolescent mice are less sensitive (Stevenson et al. 2008).

For *amphetamine*, two reports have concluded that adolescents sensitize more than adults (Adriani et al. 1998; Laviola et al. 2001). For *cocaine*, three studies have reported reduced sensitization in adolescent rats (Laviola et al. 1995; Collins and Izenwasser 2002; Frantz et al. 2007). Other studies have reported greater sensitization in adolescent rats (Caster et al. 2005, 2007) and mice (Schramm-Sapyta et al. 2004). Two of the studies which reported greater cocaine sensitization in adolescents (Caster et al. 2005, 2007) utilized rapid assessments of sensitization (within a repeated-dose binge and 24 h after a single high dose). Thus, adolescents might develop sensitization faster.

Behavioral plasticity to these drugs is clearly possible in both adolescent and adult rodents, but the relative magnitude in the two ages may depend on drug, dose, and duration of exposure. Overall, the weight of evidence shows that adolescents are not more vulnerable than adults to neuroplastic changes in the locomotor behavioral circuitry in response to intermittent repeated exposures to these drugs.

Prolonged drug exposure

Self-administration

SA of psychostimulants, nicotine, and ethanol has the potential to be an excellent model of human drug taking and the progression to dependence (THC is not reliably self-administered by rodents). Much of the research published to date has focused on the initial acquisition of SA, which is indicative of the reinforcing effects of the drugs examined. A few studies have examined long-term SA and the permutations, such as progressive ratio, LgA, extinction, and reinstatement, which are most informative about the progression to dependence.

The frequency of *nicotine* self-administration may be greater in adolescence, though results vary. Levin et al. (2003, 2007) have shown that adolescent rats take more nicotine (more infusions per hour) under a continuous reinforcement schedule (one infusion per lever press) than adult rats. This effect is highly dependent on the age of initial training within adolescence. The average number of infusions per session decreases with increasing age of onset within the adolescent age range and into early adulthood. With multiple weeks of self-administration as the animals mature, sex differences emerge. Male adolescent-onset rats show higher rates of nicotine self-administration initially but decrease their intake to adult-onset levels as they age (Levin et al. 2007). In contrast, adolescent-onset female rats show higher levels of nicotine self-administration which are maintained as they become adults (Levin et al. 2003). Another group has also shown that adolescent female rats acquire nicotine self-administration more rapidly than adult females (Chen et al. 2007). In contrast, Shram et al. have shown that at a high response ratio (five lever presses per infusion) adolescent male rats self-administer less nicotine than adults (Shram et al. 2007b). The adolescent rats in this study also exhibited less motivation to seek the drug under a progressive ratio schedule and were less resistant to extinction when saline was substituted for nicotine. Taken together, these studies suggest that adolescents might be more likely to engage in high levels of initial intake but are less likely to exhibit nicotine dependence-like behavior. See Table 1.

For *ethanol*, there are a number of studies comparing voluntary drinking in adolescent vs. adult rodents. There is some evidence that adolescent rats consume more ethanol (Doremus et al. 2005; Brunell and Spear 2005; Vetter et al. 2007), but this is not evident in all studies (Siegmund et al. 2005; Bell et al. 2006; Truxell et al. 2007) or in mice (Tambour et al. 2008). Two studies examined the effect of age on relapse and found that adolescent-onset drinkers are more susceptible to stress-induced reinstatement of drinking when examined in adulthood after long-term drinking (Siegmund et al. 2005; Fullgrabe et al. 2007), depending on the stressor used (Siegmund et al. 2005). Unlike nicotine, ethanol may induce more dependence-like behaviors in adolescent rats, regardless of the level of intake. See Table 1.

Most studies have observed no differences between adolescents and adults in levels of *cocaine* self-administration (Leslie et al. 2004; Belluzzi et al. 2005; Kantak et al. 2007; Kerstetter and Kantak 2007; Frantz et al. 2007). However, one study revealed that age differences may be dependent on genetics. Perry et al. (2007) observed that adolescent rats bred for low saccharin intake acquired self-administration faster than adults bred for low saccharin intake. In contrast, adolescents and adults bred for high saccharin intake self-administered cocaine at equivalent rates. At this point, the evidence suggests that cocaine is not self-administered at higher levels by adolescents than adults but that genetic differences may interact with age to determine the level of cocaine self-administration. See Table 1. Preliminary studies from our laboratory suggest that progressive ratio, extinction, and reinstatement of cocaine seeking do not differ between adolescent and adult rats.

These conflicting reports on the self-administration of cocaine, nicotine, and ethanol suggest that the level of voluntary intake of these drugs is not consistently age dependent. Depending on the drug examined, adolescents may be more (ethanol) or less (nicotine, cocaine) susceptible to dependence-like behaviors. Detailed studies of dependence-like self-administration behavior are key to understanding whether adolescents progress faster to compulsive patterns of drug intake. Future work should place a greater emphasis on progressive ratio, LgA, resistance to extinction, and punished or compulsive drug seeking. Such techniques have the potential to reveal whether adolescents are more prone to addiction-like behavior, distinct from their propensity for drug taking.

Withdrawal

Withdrawal is a constellation of behavioral and physiological changes that occur after cessation of intake of many abused drugs. As described above, it is characterized by physiological (diarrhea, seizures, etc.) and psychological responses (anxiety, dysphoria, craving, etc.) which can include both drug-specific responses and behaviors which may reflect a “core” aversive response (Koob 2009). The effect of withdrawal on subsequent drug taking and the progression to SUDs varies with the duration of drug intake and the experience of the user. After a single episode of drug taking, withdrawal can either reduce or increase future use. A bad hangover causes some people to avoid alcohol temporarily (Prat et al. 2008), but people who consistently have more severe hangovers and drink to alleviate hangover symptoms are more likely to progress to alcohol dependence (Earleywine 1993a, b). After repeated intake of many different drugs of abuse, symptoms such as negative affect, elevated reward threshold, and craving perpetuate continued drug taking (Koob 1996; Koob and Le Moal 1997). Several studies suggest that adolescent rodents experience reduced withdrawal symptoms for nicotine and ethanol compared to adults, as summarized below. Withdrawal from cocaine, amphetamine, and THC has not been compared in adolescent vs. adult rodents.

Many symptoms of *nicotine* withdrawal are reduced in adolescent rats, such as withdrawal-associated conditioned place aversion (O’Dell et al. 2007b), anxiety-like behavior (Wilmouth and Spear 2006; but see Kota et al. 2007), and decrements in reward (O’Dell et

al. 2006). Adolescents also show fewer somatic symptoms of nicotine withdrawal (O'Dell et al. 2006; Kota et al. 2007). See Table 1. Most *ethanol* withdrawal symptoms are also reduced in adolescent compared to adult rodents. These include withdrawal-induced social inhibition (Varlinskaya and Spear 2004a, b), anxiety-like behavior (Doremus et al. 2003), and seizures (Acheson et al. 1999). In contrast, at least two measures of withdrawal, cortical electroencephalogram activity (Slawecki et al. 2006), and hypothermia (Ristuccia and Spear 2005) are more pronounced in adolescents if ethanol is delivered by vapor inhalation. See Table 1.

It is difficult to infer from these data how the effects would generalize to human drug taking. The relative absence of withdrawal signs after prolonged exposure would be expected to slow the progression to compulsive use. In contrast, the absence of withdrawal symptoms after initial experimentation might motivate increased use due to the perception that the drug is not harmful.

Cognitive effects

There are many effects of drugs that could have a strong relationship to their abuse potential which have not yet been fully explored. For example, addicts are known to have cognitive impairments which affect their success in drug treatment (Volkow and Fowler 2000; Kalivas and Volkow 2005; Moghaddam and Homayoun 2008). It is currently unclear whether the cognitive impairments precede or result from drug taking. In addition, clinical data suggest that executive function may be impaired in both adolescents and drug addicts, facilitating the appearance of the link between the two (Chambers et al. 2003; Volkow et al. 2007; Beveridge et al. 2008; Pattij et al. 2008). Some of these effects have been examined in adolescent vs. adult rodents, which we will now summarize.

Learning and memory—Drugs of abuse can affect learning and memory acutely and could also cause persistent effects which are evident in the drug-free state. This impairment is important for several reasons which may differentially affect adolescents and adults. First, while people are under the influence of depressants such as alcohol and THC, their reaction time and judgment can be impaired (DSM-IV 1994), which could place the individual and others in their vicinity in danger. In contrast, stimulants such as nicotine and amphetamine can acutely enhance memory (Martinez et al. 1980; Provost and Woodward 1991; Levin 1992; Soetens et al. 1993, 1995; Le Houezec et al. 1994; Lee and Ma 1995; Levin and Simon 1998). After long-term use, addictive drugs may diminish cognitive ability, making recovery and treatment efforts more difficult (although it is also possible that people with preexisting diminished cognitive ability might be the most difficult to treat; Aharonovich et al. 2006; Teichner et al. 2001). Several studies in rodents have compared adolescents and adults in cognitive tasks, both acutely and after long-term exposure and abstinence. Acutely, the depressant drugs seem to impair adolescents more than adults. After long-term exposure, the effect of age of onset is drug and task specific.

Acute intoxication with *ethanol* or *THC* impairs spatial learning in the Morris Water Maze to a greater extent in adolescents (Acheson et al. 1998, 2001; Cha et al. 2006, 2007; Markwiese et al. 1998; Obernier et al. 2002; Sircar and Sircar 2005; White et al. 2000; White and Swartzwelder 2005; but see Rajendran and Spear 2004). Adolescents are also more impaired than adults by ethanol in appetitively motivated odor discrimination (Land and Spear 2004). Long-term impairment also seems to be greater after adolescent preexposure than adult preexposure. One study showed that impairment induced by *ethanol* persisted in adolescents but not adults for up to 25 days following cessation of ethanol exposure (Sircar and Sircar 2005). Similarly, performance in object recognition is more impaired after adolescent pre-exposure to *THC* (Quinn et al. 2008) and synthetic

cannabinoids (Schneider and Koch 2003; O'Shea et al. 2004) than adult preexposure. There is one contrasting study showing that the impairments caused by *THC* in spatial learning dissipate upon 4 weeks of abstinence in both ages (Cha et al. 2007).

Long-term effects of adolescent exposure have been examined in response to some psychostimulants. After extended *cocaine* self-administration and abstinence, amygdala-dependent learning is impaired to a lesser extent in adolescent-onset than adult-onset rats (Kerstetter and Kantak 2007), suggesting that adolescents may be protected from some long-term cognitive effects. In a separate study, administration of *cocaine* in early adolescence produced deficits in Morris Water Maze learning which were reversed upon long-term cocaine abstinence (Santucci et al. 2004). This study did not, however, compare the effects of adult exposure. In contrast, neurotoxic doses of *methamphetamine* produce small but long-lasting deficits in spatial learning in both the Morris Water Maze and Cincinnati Water Maze if administered between 41 and 50 days of age (late adolescence). Administration at 51–60 days had no effect (Vorhees et al. 2005).

In summary, the depressant drugs ethanol and THC *acutely* impair adolescents more than adults. This may affect decision making while users are under the influence of the drugs. Studies of the acute effects of stimulants on cognitive ability would be informative. *Long-lasting* effects seem to be drug specific: persistent effects of alcohol, THC, and neurotoxic doses of methamphetamine have been described, although there are conflicting reports. These studies raise the concern that long-lasting cognitive impairment from adolescent drug exposure, particularly depressants, could raise vulnerability to future drug use.

Impulsivity and executive function—SUDs are often conceptualized as a failure of impulse control or executive function: addicts fail to control the impulse to take drugs despite adverse consequences. They also fail to plan ahead and make decisions in their best interests (Kalivas and Volkow 2005). The loss of executive control in addiction is thought to result from reduced glutamatergic drive from the prefrontal cortex to the nucleus accumbens in response to natural rewards and an excess drive in response to drug-associated stimuli (Kalivas and Volkow 2005). Adolescents are known to have reduced activity of the "supervisory system," the prefrontal cortex (Ernst et al. 2006), and adolescent humans have immature prefrontal cortical circuitry (Lenroot and Giedd 2006). In this sense, adolescents may have deficient executive function, even without drug exposure. *THC* has been shown to impair executive functioning (Egerton et al. 2005, 2006) in tasks dependent upon the prefrontal cortex (McAlonan and Brown 2003), but no experiments published to date have examined whether this effect is age specific.

Impulsivity is a complex concept, and most researchers divide it into multiple domains (Evenden 1999). In rodents, impulsivity is most often modeled using three types of tasks. First, delay discounting procedures require the animal to choose between a small immediate reinforcer and a larger delayed one. In such models, *cocaine* and *amphetamine* increase impulsive choice (Paine et al. 2003; Helms et al. 2006; Roesch et al. 2007), and rats bred for high *alcohol* consumption tend to exhibit greater impulsivity (Wilhelm and Mitchell 2008). Adolescents are more impulsive in such tasks at baseline (Adriani and Laviola 2003). *Nicotine* exposure during adolescence does not adversely affect performance in this task when tested in adulthood (Counotte et al. 2009). Another aspect of impulsivity is modeled by the fixed consecutive number (FCN) task and Go/No-go task. These tasks assess the ability to inhibit an improper response while performing an appropriate one. *Ethanol* and *amphetamine* increase impulsivity in the FCN task (Evenden and Ko 2005; Bardo et al. 2006). *Cocaine* does not influence behavior in the Go/No-go task (Paine et al. 2003). Mice bred for high *alcohol* consumption exhibit greater impulsivity in the Go/No-go task (Wilhelm et al. 2007). A third type of impulsivity is modeled in the differential

reinforcement of low rates of responding (DRL) task. It models the ability to wait before seeking reinforcement. *Cocaine* (Wenger and Wright 1990; Cheng et al. 2006), *amphetamine* (Wenger and Wright 1990), and *ethanol* (Popke et al. 2000; Arizzi et al. 2003) increase impulsivity in the DRL task. The effect of adolescence on the response to drugs in all of these tasks is a critical area for future study, as developmental stage itself may be a significant vulnerability in this domain.

Role of pharmacokinetics in behavioral measures

Several pharmacokinetic properties of drugs of abuse could contribute to development of dependence. The rates of appearance and clearance of the drug in the brain (and at its molecular targets), the peak concentration, and the duration of exposure can affect the addictive effects of drugs (Sellers et al. 1989; de Wit et al. 1992; Gossop et al. 1992). Euphorigenic effects of drugs are enhanced by rapid accumulation in brain (de Wit et al. 1992; Abreu et al. 2001; Nelson et al. 2006). Although less studied, the aversive, reinforcing, and cognitive effects of drugs of abuse could be similarly affected by these pharmacokinetic variables. Rate of drug delivery is determined by the drug itself, the formulation, and the chosen route of administration. Studies comparing adult and adolescent pharmacokinetics of common drugs of abuse are sparse and not yet comprehensive with respect to dose, route of administration, and timing. The most informative studies have examined behavioral effects and pharmacokinetics in parallel and generally demonstrated that age differences in behavior are not related to varying drug levels.

Nicotine and its metabolite, *cotinine*, which may also be biologically active (Terry et al. 2005), are metabolized faster in adolescent than in adult rats (Slotkin 2002). However, in two studies in which nicotine dosing was adjusted to achieve comparable plasma levels, adolescents still exhibited reduced signs of withdrawal (O'Dell et al. 2006, b). *Ethanol* seems to enter the brain and blood at similar rates and extents in adolescents and adults (over a range of 5–30 min; Varlinskaya and Spear 2006) but it is cleared more rapidly from adolescent than from adult rodents, over a range of 2–18 h (Doremus et al. 2003). However, differences in sedation are not attributable to the difference in clearance. Little et al. (1996) showed that adolescent rats lose their righting reflex for a shorter duration than adults but, upon awakening, have higher blood alcohol levels. Similarly, age differences in locomotor sensitization to ethanol are independent of blood alcohol levels (Stevenson et al. 2008). *Methamphetamine* stimulates locomotor activity to a lesser extent in adolescent than adult mice despite achieving comparable brain concentration (Zombeck et al. 2009). For *cocaine*, one group has observed that adolescent mice have lower levels in blood and brain at 15 min postinjection than adults (McCarthy et al. 2004). In contrast, another group has shown higher levels at 5 min (Zombeck et al. 2009) despite observing reduced locomotor stimulation. Our group has measured equivalent levels in brain tissue and lower levels in blood in adolescents compared to adults despite the fact that we observed increased locomotor responses in adolescent rats (Caster et al. 2005). In summary, there are reports of differing pharmacokinetic profiles in adolescent vs. adult rodents, but they do not account for age-related behavioral differences.

Neurobiological considerations

The behavioral studies summarized above point to the conclusion that adolescents may tolerate higher and more frequent drug exposures, but there are not yet enough data to show whether they are more likely to develop compulsive patterns of drug taking and dependence-like behavior. Additional studies with more comprehensive models of drug dependence are necessary to confirm or refute this speculation. In addition, an understanding of the molecular and neurophysiological basis of drug dependence is key to determining whether

the process happens more rapidly or extensively in adolescents. A large body of research is aimed at understanding the physiological basis of drug dependence. These findings have been extensively reviewed elsewhere (Robinson and Berridge 1993; 2000; Nestler 1994; Fitzgerald and Nestler 1995; Nestler et al. 1996; Volkow and Fowler 2000; Koob and Le Moal 2001; Hyman and Malenka 2001; Shalev et al. 2002; Winder et al. 2002; Goldstein and Volkow 2002; Kalivas and Volkow 2005; Yuferov et al. 2005; Grueter et al. 2007; Kalivas and O'Brien 2008). They provide a framework for evaluating molecular and neurophysiologic mechanisms that might mediate substance abuse vulnerability in adolescents.

Several studies have tested whether there are molecular and physiological differences between adolescents and adults that might underlie differential vulnerability to drug dependence (see (Schepis et al. 2008) for review). In general, molecular and physiological studies have revealed mechanisms that could be related to age differences in sensitivity to drug reward, but evidence about neuroplastic events related to the transition to compulsive drug use does not yet exist. The initial rewarding effects of drugs of abuse are dependent upon dopaminergic signaling. Adolescents have rapidly maturing dopaminergic neurocircuitry in the areas related to drug reward, in terms of presynaptic and postsynaptic function such as dopamine transporter and receptor expression (Seeman et al. 1987; Palacios et al. 1988; Teicher et al. 1995; Tarazi et al. 1998a, [b], [1999]; Meng et al. 1999; Montague et al. 1999; Andersen et al. 2002; Andersen 2003, 2005) and dopamine content in brain tissue (Andersen 2003, 2005). These studies have shown that innervation of the forebrain continues through adolescence, with levels of terminal markers such as dopamine content, transporters, and synthetic enzymes reaching a peak in late adolescence. Postsynaptic receptor number peaks and then declines to adult levels as innervation becomes complete. Most studies show that basal levels of synaptic dopamine are lower during this phase of development (Andersen and Gazzara 1993; Badanich et al. 2006; Laviola et al. 2001; but see Camarini et al. 2008; Cao et al. 2007b; Frantz et al. 2007) which is consistent with incomplete innervation. Adolescents also differ from adults in the amount of dopamine released in response to amphetamine and cocaine: the percentage change in extracellular dopamine level is greater in adolescents than adults (Laviola et al. 2001; Walker and Kuhn 2008; but see Badanich et al. 2006; Frantz et al. 2007), and the rate of increase may be faster in adolescents (Badanich et al. 2006; Camarini et al. 2008). In these studies, one critical determinant of the experimental results is the age at which the experiment was conducted: dopamine systems in early adolescence (day 28) are very different from those in late adolescence (day 42) and at the beginning of adulthood (day 60).

These neurobiologic differences between adolescents and adults are often not concordant with behavioral measures. For example, psychostimulant sensitization is reduced in adolescents despite greater increases in dopamine (Laviola et al. 2001; Frantz et al. 2007), while conditioned place preference is greater in adolescents despite comparable increases in dopamine (Badanich et al. 2006). One study that did observe concordance between dopamine release and intravenous self-administration reported no age difference in either measure (Frantz et al. 2007).

Similarly inconclusive findings have also been reported regarding the molecular and physiological responses to prolonged drug taking. Prolonged exposure leads to a decrease in the induction of immediate early genes (such as c-fos), upregulation of other genes, and the accumulation of long-lived proteins like delta Fos B, which persist for days or weeks (Kalivas and O'Brien 2008). These changes accompany and may mediate synaptic rearrangement in cortical circuitry and dysregulated glutamatergic signaling which are thought to underlie pathological drug seeking. A few studies have examined induction of c-fos in response to drugs of abuse in adolescents vs. adults, and the results are highly variable

and dependent upon the brain region examined, stimulant used, and dose. Shram et al. observed that after low-dose (0.4 mg/kg) but not high-dose (0.8 mg/kg) *nicotine*, adolescents expressed greater c-fos in the medial nucleus accumbens shell (Shram et al. 2007a). Similar dose specificity of age effects has been reported for cocaine. Three studies have shown that adults generate more c-fos expression than adolescents in a few striatal subregions after high-dose (30–40 mg/kg) *cocaine* (Kosofsky et al. 1995; Cao et al. 2007b; Caster and Kuhn 2009). In contrast, adolescents have greater responses throughout the dorsal striatum and medial shell of the nucleus accumbens in response to lower-dose cocaine (10 mg/kg; Caster and Kuhn 2009). In many brain regions, however, fos induction is similar between the two ages (for *nicotine* amygdala, locus coeruleus, lateral septum, superior colliculus (Cao et al. 2007a; Shram et al. 2007a) and for *cocaine* bed nucleus of the stria terminalis (Cao et al. 2007b), cortex, and cerebellum (Kosofsky et al. 1995)). The stable protein product of the fos gene, delta Fos B, is also regulated in a drug- and region-specific manner. Upon treatment with *nicotine*, one group has reported no age effect (Soderstrom et al. 2007). After *cocaine* or *amphetamine*, adolescents express more delta Fos B in the nucleus accumbens and caudate putamen (Ehrlich et al. 2002). In general, the current studies are inconclusive about whether the molecular changes thought to be important for the transition to compulsive drug taking are exaggerated in adolescents.

The long-term behavioral effects of repeated drug taking are likely mediated by altered synaptic efficacy brought about by structural and biochemical mechanisms. Dendritic arbors in the nucleus accumbens and prefrontal cortex are altered after long-term *cocaine* and *amphetamine* exposure (Robinson and Kolb 2004), but these alterations have not yet been compared in adolescents vs. adults. After exposure to *nicotine*, dendritic length is differentially affected in adolescent vs. adult rats in the prelimbic cortex (Bergstrom et al. 2008) and nucleus accumbens (McDonald et al. 2007). The functional significance of these differences remains to be elucidated.

Electrophysiological responses can also be altered by drugs of abuse. For example, studies in adult rodents have shown that repeated self-administration or experimenter administration of *cocaine* reduces glutamatergic synaptic strength in the nucleus accumbens (Thomas et al. 2001; Schramm-Sapyta et al. 2005) and reduces long-term depression in the bed nucleus of the stria terminalis (Grueter et al. 2006). These alterations parallel altered expression levels of *α*-amino-3-hydroxyl-5-methyl-4-iso-xazole-propionate and *N*-methyl-D-aspartic acid receptors (Lu et al. 1997, 1999; Lu and Wolf 1999). Adolescent rats are generally more susceptible to plasticity in the nucleus accumbens (Schramm et al. 2002) and in many other brain regions (Kirkwood et al. 1995; Izumi and Zorumski 1995; Crair and Malenka 1995; Liao and Malinow 1996; Partridge et al. 2000) in response to electrical stimulation and could therefore be more susceptible to the effects of cocaine. The electrophysiological response of this circuit to drugs of abuse presents a potential mechanism for enhancing adolescent susceptibility to SUD but has not been directly compared in adolescent vs. adult animals. Many other potential mechanisms remain unexplored in adolescents vs. adults at this time, such as glutamate receptor expression (Lu et al. 1999; Lu and Wolf 1999) and chromatin remodeling (Kumar et al. 2005). If behavioral studies conclusively reveal that adolescent onset is causal in the progression to compulsive drug seeking, then these mechanisms should be explored.

Future studies should focus on linking molecular and physiological studies with relevant behavioral models to address which molecular alterations are most relevant to drug dependence and asking whether the currently identified differences between adolescents and adults might cause differences in behaviors related to SUD.

Summary

In this review, we have addressed the question of whether adolescents are more vulnerable to drug addiction than adults by summarizing results from animal studies. These studies suggest four conclusions:

1. The balance of rewarding vs. aversive effects of drugs of abuse is tipped toward reward in adolescents, as shown in place preference, place aversion, and taste aversion studies. This could increase consumption of drugs of abuse by adolescents.
2. Adolescents are consistently less sensitive to withdrawal effects. This could both promote drug use in early stages and protect against development of compulsive drug seeking after long-term use.
3. Adolescents are not consistently more sensitive to reinforcing or locomotor effects of drugs of abuse as shown in self-administration and sensitization studies.
4. Adolescents are undergoing changes in neuronal structure and function in brain areas related to reward and habit formation, which could influence susceptibility to drug dependence, although studies demonstrating causality are currently lacking.

These studies suggest that adolescents experience a different “balance” of rewarding and aversive effects of drugs of abuse. This balance could represent a potential vulnerability for increased experimentation. However, one critical element is missing in our ability to evaluate the risk of adolescent vulnerability to SUD. There are few data about the progression to compulsive drug seeking, the hallmark of drug dependence. It is imperative to more fully explore animal models of the progression to drug dependence to address whether adolescents develop compulsive use more frequently or rapidly than adults and whether adolescents are more or less resistant to extinction and reinstatement of drug taking. Second, more studies of the effects of adolescent exposure on cognitive function, particularly related to executive control, are warranted. Third, studies of molecular alterations in response to drugs of abuse in adolescents vs. adults are incomplete and inconclusive. As animal models of the progression to addiction become better understood and developed, molecular alterations underlying this transition can be explored in greater depth and the functional implications of these effects can be determined.

Finally, a key direction for future research is the intersection between age-related and individual differences. Human studies (Dawes et al. 2000) and some animal studies (Barr et al. 2004; Perry et al. 2007) suggest that genetics, environment, and psychopathology contribute to early drug taking and development of addiction. A better understanding of this relationship will greatly benefit prevention and treatment efforts: when we can determine who is most likely to become addicted and why, then we can prevent and treat drug problems in those individuals most successfully, regardless of when they initiate drug use.

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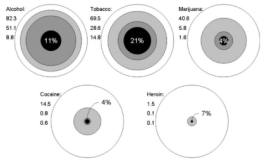

Fig. 1.

Percentages of the US population over the age of 12 years who have ever tried the indicated drug (*top number*, *light gray circle*); who used the indicated drug in the past month (*middle number*, *darker gray circle*); who meet criteria for dependence on the indicated drug (*bottom number*, *black circle*). *Numbers* in the *center* of each *diagram* represent the percentage of people who have ever tried the indicated substance who are currently dependent. Data obtained from the NSDUH 2007, lifetime use, past month use, DSM-IV dependence criteria (for all drugs except tobacco), and daily cigarette use (for tobacco)

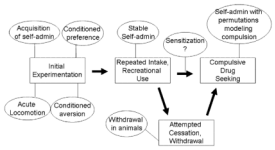

Fig. 2.

Stages in the progression to drug dependence (*rectangles*) and animal models related to each stage (*ovals; self-admin*, self-administration)

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Table 1

Age dependence of reward, aversion, self-administration, and withdrawal

		Cocaine	Amphetamine	Nicotine	Ethanol	THC
Reward	Reward greater in adolescents	Badanich et al. 2006; Brenhouse et al. 2008; Brenhouse and Andersen 2008; Zakharova et al. 2008a, b		Belluzzi et al. 2004; Brielmaier et al. 2007; Shram et al. 2006; Torrella et al. 2004; Vastola et al. 2002; Kota et al. 2007; Torres et al. 2008	Philpot et al. 2003	
	Reward greater in adults	Aberg et al. 2007; Balda et al. 2006	Adriani and Laviola 2003			
	No age effect on reward	Schramm-Sapyta et al. 2004; Campbell et al. 2000	Torres et al. 2008			
Aversion	Aversion greater in adults	Schramm-Sapyta et al. 2006	Infurna and Spear 1979	Shram et al. 2006; Wilmouth and Spear 2004	Philpot et al. 2003; Schramm-Sapyta, unpublished	Schramm-Sapyta et al. 2007; Quinn et al. 2008
Self-administration	Adolescents self-administer more, acquire faster, exhibit more motivation, or exhibit greater relapse	Perry et al. 2007 (LoS rats)		Levin et al. 2003, 2007; Chen et al. 2007	Brunell and Spear 2005; Doremus et al. 2005; Vetter et al. 2007; Fullgrabe et al. 2007; Siegmund et al. 2005	
	Adults self-administer more, acquire faster, exhibit more motivation, or exhibit greater relapse			Shram et al. 2007b		
	No age effect on self-administration	Perry et al. 2007 (HiS rats); Belluzzi et al. 2005; Frantz et al. 2007; Kantak et al. 2007; Kerstetter and Kantak 2007; Leslie et al. 2004			Bell et al. 2006; Siegmund et al. 2005	
Withdrawal	Adolescents have less severe withdrawal			O'Dell et al. 2007a, b; Wilmouth and Spear 2006; O'Dell et al. 2006; Kota et al. 2007	Varlinskaya and Spear 2004a, b; Doremus et al. 2003; Acheson et al. 1999	
	Adults have less severe withdrawal				Slawecki et al. 2006; Ristuccia and Spear 2005	

Studies cited (see text) demonstrating the indicated effect for the indicated substance