THE RELATIONSHIP OF IMPULSIVE AND DYSREGULATED BEHAVIORS TO SUBSTANCE USE

by

SETH CHARLES HARTY

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2011

This manuscript has been read and accepted for the
Graduate Faculty in Psychology in satisfaction of the
dissertation requirement for the degree of Doctor of Philosophy.

Date	Jeffrey M. Halperin, Ph.D. Chair of Examining Committee
Date	Maureen O' Conner Executive Officer

Robert Ranaldi, Ph.D.

Janine Flory, Ph.D.

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

THE RELATIONSHIP OF IMPULSIVE AND DYSREGULATED BEHAVIORS TO SUBSTANCE USE

by

Seth Charles Harty

Adviser: Jeffrey M. Halperin, Ph.D.

Longitudinal studies indicate that individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD) in childhood exhibit elevated rates of substance use and substance use disorders (SUDs) during adolescence and young adulthood (Mannuzza et al., 1998; Schubiner et al., 2000a; Elkins et al., 2007a; Milberger et al., 1997). The subsequent development of substance use in individuals with ADHD has been found to be largely impacted by the presence of comorbid conduct disorder (CD), (Barkley et al., 1990; Molina & Pelham, Jr., 2003; Molina et al., 2002). However, several studies have shown an association between ADHD and increased substance use over and above the risk posed by CD (Burke, Loeber, & Lahey, 2001; Elkins et al., 2007; Milberger et al., 1997) whereas others have suggested that CD mediates the relationship between ADHD and later substance misuse (Brook et al 2010). The diagnostic criteria for CD, ADHD, Substance Abuse and Substance Dependence are notable for the presence of impulsive and dysregulated behaviors (American Psychiatric Association, 2000). Additionally, one of the most robust and consistent predictors associated with maladaptive substance use is a persistent pattern of impulsive behavior (Littlefield, Sher, & Steinley, 2010).

The series of studies that comprise this dissertation investigated further the relationship between substance use and impulsive/dysregulated behavior using animal models of impulsivity and longitudinal studies of youth with ADHD. Study I employed animals and measured the degree to which impulsive behavior, as characterized by performance on a delay discounting paradigm for food reward, was impacted after chronic drug (heroin) administration. Studies II and III characterized substance use outcomes as a function of impulsive and dysregulated behaviors and psychostimulant treatment in a large sample of ethnically diverse, lower SES urban youth diagnosed with ADHD in childhood and a community matched control group. Study II examined late adolescent substance use outcomes in relation to childhood conduct disorder (CD) and psychostimulant treatment in youth diagnosed with ADHD in childhood and Study III examined the degree to which childhood and adolescent ratings of aggression, delinquency and attention are differentially related to adolescent substance use outcomes.

Results of these studies serve to further clarify the relations between impulsive behaviors and maladaptive substance use. Study I did not provide support for the idea that impulsivity is caused by drug use. However, Study II reported robust findings indicating that the dysregulated behaviors associated with childhood diagnoses of CD, and not ADHD, portend both greater substance use severity and impairment. Further, a diagnosis of CD is characterized by both delinquent and aggressive behaviors and Study III provided evidence that delinquency, but not aggression, is the most robust predictor of adolescent substance use outcome.

The findings from this dissertation have important implications with regard to delinquent behaviors and substance use outcomes. As such, identifying and targeting impulsive behaviors related to the expression of delinquency may be a focus of continued efforts in the areas of preventative and psychosocial treatments.

Table of Contents

List of Charts

List of Figures

GENERAL INTRODUCTION

Impulsive and Dysregulated Behaviors and Substance Use

Maladaptive substance use, including, but not limited to, the diagnostic categories of abuse and dependence, have negative consequences for individuals and for society. According to the National Institute on Drug Abuse (NIDA), the overall annual cost of maladaptive substance use in the United States was recently estimated to exceed $600 billion dollars. This estimate includes the loss of work productivity and health related costs, as well as expenses attributable to substance use related crime (see Understanding Drug Abuse and Addiction, www.nida.nih.gov). However, such estimates fail to fully account for the intra- and inter-personal impact substance misuse has on individuals and families. Research aimed at gaining a better understanding of the etiology of problematic substance use is critically important to the successful formulation of preventative interventions. Problems with the regulation of affect, behavior, and cognition, often first seen in childhood, have been repeatedly associated with substance use (Brook, Whiteman, Finch, & Cohen, 1996; Hawkins, Catalano, & Miller, 1992; Tarter et al., 1999). Gaining a better understanding of these behaviors of psychological dysregulation will help to inform future intervention strategies.

Substance Use: General Characteristics and Etiologic Factors

Substance use disorders (SUDs) are categorized into separate groupings of abuse and dependence as they pertain to 11 classes of substances (alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, and sedatives/hypnotics/anxiolytics (American Psychiatric Association, 2000). Substance

Abuse is defined as a maladaptive pattern of use that results in a recurrent pattern of consequences associated with the continued use of substances over a 12 month period of time. Substance Dependence is classified as a collection of symptoms resulting from continued and prolonged substance use. Such use may result in compulsive drug taking and the physiological symptoms of withdrawal and/or tolerance.

Maladaptive substance use, across drug classes, is associated with a number of poor outcomes such as a decline in physical and mental health, reduced economic attainment, reduced use of medical and mental health services, work related difficulties, and lower self regard (Pujazon-Zazik & Park, 2009; Rogers et al., 2009; Schempf, 2007; Sher, Grekin, & Williams, 2005; Stalnaker, Takahashi, Roesch, & Schoenbaum, 2009; Vitale & Van de Mheen, 2006). Recent epidemiologic studies indicate that 10.3% of individuals meet lifetime criteria for a SUD other than alcohol abuse or dependence (Compton, Thomas, Stinson, & Grant, 2007) while 30.3% of individuals reported ever having met criteria for an alcohol related disorder (Hasin, Stinson, Ogburn, & Grant, 2007). Substance use related difficulties are likely to continue and results from the annual Monitoring the Future national survey of high school students indicates that substance use continues to be a popular behavior such that, in 2010, 54.1% of high school seniors reported ever drinking to drunkenness while 48.2% reported ever using an illicit substance, including marijuana (Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E., 2011). Thus, the established poor outcomes associated with long-term substance use, combined with the prevalence of individuals engaging in substance using behaviors, indicates that substance use continues to pose a significant public health concern. According to the 2009 National Survey on Drug Use and Health by the

Substance Abuse and Mental Health Services Administration (Substance Abuse and Mental Health Services Administration, 2010) individuals 18-20 years of age reported the highest rate of illicit drug use. As such, adolescence/young adulthood may be considered a developmental period of risk and, thus, an appropriate age to examine substance use outcomes.

Previous studies have revealed a vast array of variables that predict later maladaptive substance use. Social environmental factors such as those associated with intrafamilal dynamics (Cohen & Rice, 1997; Galaif, Stein, Newcomb, & Bernstein, 2001), peer group affiliation (Dinges & Oetting, 1993), and issues of socio-economic status (Miller & Miller, 1997) including neighborhood and level of drug availability; as well as genetic susceptibility (Clark et al., 1997), and intrapersonal factors such as personality traits (Elkins, King, McGue, & Iacono, 2006), externalizing behaviors (Hayatbakhsh et al., 2008; Mayzer, Fitzgerald, & Zucker, 2009; Molina et al., 2007), and psychiatric status (Barkley, Fischer, Edelbrock, & Smallish, 1990; Biederman, 2003; Boyle et al., 1993; Chilcoat & Breslau, 1999; Hayatbakhsh et al., 2008; Mayzer et al., 2009; Milberger, Biederman, Faraone, Chen, & Jones, 1997; Molina, Bukstein, & Lynch, 2002) have all been shown to be predictive of later substance use involvement

One of the most robust and consistent predictors to have been associated with maladaptive substance use and the diagnostic outcomes of abuse and dependence is a persistent pattern of impulsive behavior (Littlefield, Sher, & Steinley, 2010). Impulsivity, which is a term often used interchangeably with “behavioral undercontrol,” “dysregulation” and “disinhibition” (Evenden, 1999), is closely linked to many of the predictor variables previously listed and is the topic we turn to now.

Impulsivity: General Characteristics

There are a number of ways to define the construct of impulsivity (Evenden, 1999). A broad definition conceptualizes impulsivity as immaturely conceived behaviors that are prematurely expressed and are often risky, socially inappropriate, and frequently result in less than desirable outcomes (Evenden & Ryan, 1996). Thus, impulsivity is a constellation of interrelated behaviors characterized by a difficulty in inhibiting behavioral responses (Elkins et al., 2006) and, problems with the regulation of affect, behavior, and cognition. These difficulties are often first seen in childhood and have been repeatedly associated with adolescent/young adult substance use (Clark, Cornelius, Kirisci, & Tarter, 2005; Hicks, Iacono, & McGue, 2010; Clark, Thatcher, & Tapert, 2008; Tarter et al., 2003; Tarter, Kirisci, Habeych, Reynolds, & Vanyukov, 2004) . As suggested above, there are a number of factors that influence behaviors that can be described as impulsive. As of yet, no experimental model has been devised to account for all varieties of impulsive behavior. In his review of the different types of impulsive behavior, Evenden (1996) concludes that, while some researchers have attempted to characterize behavior defined as impulsive to one primary factor, most have ultimately stated that an acceptable explanation demands several independent factors. At its most basic, different manifestations of impulsive behavior may be considered to manifest out of dysregulated affective and/or cognitive processes (Evenden,1996). Affective impulsivity refers to an individual's inability to monitor and inhibit high emotional experiences. Affective impulsivity has often been measured as frustration tolerance, i.e. the degree to which an individual either reports or is observed being able to tolerate frustrating situations, ability to delay gratification, and risk taking and novelty seeking.

Cognitive impulsivity is also related to difficulties in inhibition, but in the absence of a strong affective response. Measures designed to assess cognitive impulsive behaviors have often focused on response inhibition. A commonly used measure of response inhibition is the Go/No-go test. The Go/No-go is used to measure response control where a participant is required to inhibit a prepotent motor response.

Impulsivity and SUD

Impulsive behaviors are implicitly associated with diagnoses of both Abuse and Dependence. The diagnostic symptoms of Abuse, as defined by DSM-IV (recurrent use in physically dangerous situations, repeated legal problems, and repeated failure to fulfill role obligations), clearly show a maladaptive pattern of behavior resulting from, in part, lack of planning and poor judgment. However, symptoms of Dependence focus more on the insidious and compulsive nature of substance related behaviors (Tolerance, Withdrawal, inability to control use, and the increase in time spent obtaining and recovering from use). Research in adolescent and young adult substance users shows that deficits in impulsivity are associated with maladaptive use severity and ratings of both abuse and dependence (Bickel & Marsch, 2001; Sussman, McCuller, & Dent, 2003). Therefore, irrespective of diagnosis, ratings of impulsivity should differentiate individuals with a SUD from non-substance using controls.

The relationship between impulsivity and SUD status is complicated by the fact that a number of comorbid psychiatric diagnoses, which are also linked to impulsivity, are associated with adolescent and young adult substance use and SUD. A review of 22 articles examining psychiatric comorbidity in community samples of adolescent substance users found that approximately 60.0% of substance using adolescents (with and without a diagnosis of SUD) met criteria for some form of non-drug-related psychiatric diagnosis, with the most prevalent being the Disruptive Behavior Disorders (DBDs): Conduct Disorder (CD), Oppositional Defiant Disorder (ODD), and, to a lesser extent, Attention Deficit Hyperactivity Disorder (ADHD) (Armstrong & Costello, 2002). Additionally, among college students, James and Taylor (James & Taylor, 2007) showed that impulsivity was associated with both substance use and ratings of Cluster B Personality Disorders. Interestingly, at the symptom level, the childhood DBDs (i.e., ODD and CD), ADHD, and adult Cluster B Personality Disorders are all characterized by impulsive symptomatology (American Psychiatric Association, 2000), raising the possibility that maladaptive patterns of drug use are naturally occurring consequences of pre-existing deficits in behavioral regulation.

Neurobiology of SUD and Impulsivity

While the explicit nature of the relationship between impulsivity and drug abuse remains unclear, the degree of association suggests that an overlap between neurotransmitter systems and neuroanatomical structures likely exist. In their review of the neurobehavioral mechanisms of impulsivity, Dalley et al. (2008) provides a functional neuroanatomical model of brain regions implicated in impulsive behavior. This system consists of cortical-ventral and striatial brain areas. The orbitofrontal cortex (OFC), medial prefrontal inframbic cortex (IL), anterior cingulate cortex (ACC), and the shell of the nucleus accumbens (NAcbS) are all innervated by the locus coeruleus (LC) and ventral tegmental area (VTA), the latter of which also projects to the nucleus accumbens core (NAcbC). The LC, located in the dorsal wall of the rostral pons, is the principal site for norepinephrine (NA) synthesis and the VTA is one of the main nuclei in the dopaminergic (DA) system. Acting as a feedback loop, descending cortical pathways from the OFC, Acc, and IL terminate in NAcbS, NAcbC, VTA, and LC.

Relatedly, the neural structures that have been implicated in drug abuse and addiction form a limbic-cortical system that is common in both drug and non-drug reward, and involves the VTA , NAcb, medial prefrontal cortex (mPFC), amygdala, hippocampus, and striatum (Wise & Bozarth, 1987; Wise, 2000). While the mesolimbic DA system has been the focus of much of the research on drug abuse and reward, it is clear that reward function in general, as well as in relation to drug use, involves the mesocortical, and nigrostriatal DA systems as well (Wise, 2005).

By far, the neurotransmitter most commonly implicated in drug abuse and impulsivity is dopamine. The following is an overview of the current understanding of the DA systems as it corresponds to impulsivity and drug abuse.

Dopamine

Different substances of abuse variably impact receptor systems. However, it is generally felt that the universal action on the reward-related dopamanergic system is a critical part of the addictive process (Wise & Bozarth, 1987; Wise, 2000; Wise, 2004; Wise, 2005). In particular, drugs of abuse have been shown to increase extracellular levels of DA in both the NAcb (Imperato & Di Chiara, 1986; Pidoplichko, DeBiasi, Williams, & Dani, 1997) and mPFC (Wise & Bozarth, 1987). Together, the neural structures that have been implicated in drug abuse and addiction form a limbic-cortical system that is common in both drug and nondrug reward (Wise, 2004). As previously indicated, the mesocorticolimbic system originates in the VTA and projects to the NAcb, amygdala, hippocampus, and cortical areas such as the mPFC. These structures, in turn, send reciprocal afferent projections back to the VTA and NAcb (Wise, 2004; You, Wang, Zitzman, Azari, & Wise, 2007). Additionally, the nigrostriatal DA system, originating in the substantia nigra and projecting to the striatum, has been shown to be involved in drug reward as animals exhibit increased stereotypic movements in response to high doses of a number of drugs of abuse (Wise & Bozarth, 1987).

It is important to note that attributing drug reward and addiction solely to the DA system is grossly simplifying a very complex cascade of behaviors that are just beginning to be understood. Dopamine may be the most visible neurotransmitter implicated in drug use, but its function is mediated/moderated by a number of different neurotransmitters including, but not limited to, muscarinic and glutamatergic input to the VTA, nicotinic, muscarinic, $GABA_A$, and delta opioid receptors at the VTA (Wang, You, Rice, & Wise, 2007; Wise, 2000; Wise, 2005).

There are currently five recognized DA receptor subtypes comprising two subtype families. The D_1 subtype family consists of D_1 and D_5 receptors, and the D_2 subtype family is comprised of D_2, D_3, D_4 receptor subtypes (Le Foll, Gallo, Le Strat, Lu, & Gorwood, 2009). Both the D_1 and D_2 receptor subtypes which are widely distributed throughout the ventral and dorsal striatum have been implicated in mediating the rewarding effects of drugs of abuse. Understanding the independent effects of these receptors has been difficult as current antagonists and agonists often lose specificity at high doses (Le Foll et al., 2009). While relatively little is known about the D_4 and D_5 subtypes in relation to drug abuse, and D_4 deficient mice are not more impulsive compared to controls (Helms, Gubner, Wilhelm, Mitchell, & Grandy, 2008), the D_3

subtype, which is more specifically expressed in the NAcb in rodents, is thought to impact the motivational behavior associated with drug use (Le Foll et al., 2009).

According to a review by Cardinal (Cardinal, 2006), interest in DA and impulsivity was first generated as a result of findings that amphetamine and other psychostimulants, substances that positively impact DA efflux and can prevent reuptake, were effective therapies for individuals with ADHD. However, animal studies examining impulsive behavior as a function of acute stimulant administration have yielded conflicting findings with some studies showing reductions in impulsive responding (de Wit, Enggasser, & Richards, 2002; Isles, Humby, & Wilkinson, 2003; Wade, de Wit, & Richards, 2000) while others show the opposite effect (Evenden & Ryan, 1996). Such discrepancies suggest that differences in methodology and dose strength may impact findings. Richards (Richards, Sabol, & de Wit, 1999) showed that while low doses (.5, 1.0, 2.0 mg/kg) of methamphetamine administered before testing resulted in less impulsive responding, animals administered 4.0 mg/kg 22 hours before testing were more impulsive when compared to saline treated animals. Aside from the important methodological considerations surrounding dose amounts highlighted above, it has been suggested that the presence of cues during delay reward trials may impact impulsive responding as such signals have been shown to increase delay lever responses in rats (Cardinal, Robbins, & Everitt, 2000).

The review of neural structures associated with both impulsivity and reward processes related to maladaptive substance use suggest that these systems, while distinct, partially overlap. It may be that the strongest association between drug use and impulsivity exists in the disruption/deficiencies of the shared anatomical structures such as the NAcb/ventral striatum. The degree to which trait impulsivity predicts later drug use, the degree to which impulsivity is predicted by drug use, and the possibility that both drug use and impulsive choice can be attributed to a third factor is the focus of the next section.

Does pre-occurring impulsivity cause drug misuse?

Clinical Studies

Mischel (Mischel, Shoda, & Peake, 1988) published a landmark study investigating adolescent outcome as a function of preschool delay of gratification measured by a child's ability to wait for a reward pre-selected by the child. Results indicated that individuals who were able to wait longer when they were between the ages of 4-5 years had better parent rated cognitive, academic, and social functioning competencies approximately 10 years later. It is remarkable that a unitary measure of functional performance such as self-imposed delay of gratification could be predictive of such developmental outcomes.

Prospective longitudinal studies examining the adolescent and young adult outcome of children diagnosed with ADHD have implicated impulsivity, and to a lesser extent hyperactivity and inattention, as predictors of later SUD outcomes (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Schubiner et al., 2000; Elkins, McGue, & Iacono, 2007; Milberger et al., 1997a). Outcome measures have been found to be significantly impacted by ADHD severity as well as the presence of co-occurring psychopathology; a diagnosis of childhood ADHD with co-morbid CD has been shown to clearly predict later substance use (Barkleyet al., 1990e; Molina & Pelham, Jr., 2003; Molina et al., 2002). As such, the association between early ADHD and later substance use is often confounded by the presence of comorbid DBDs such as CD (Boyle et al., 1993). However, after controlling for CD, some adolescent follow-up studies of children with ADHD show elevated rates of substance use (Elkins et al., 2007; Molina & Pelham, Jr., 2003)**.** The drawback to these methodologically sound studies, as they pertain to the topic of impulsivity and drug use, is that ADHD is a multi-symptomatic psychiatric diagnosis, consisting of maladaptive patterns of inattention, impulsivity, and hyperactivity, each defined by an independent constellation of behaviors (American Psychiatric Association, 2000). The same can be said for the diagnosis of CD, which consists of both delinquent and aggressive behaviors.

As such, while studies indicate that diagnoses of childhood ADHD and/or CD portend later substance use, it is difficult to separate the specific contribution of impulsivity as an independent construct. Additionally, as individuals with ADHD frequently present with a series of comorbid psychiatric disorders (Biederman, Newcorn, & Sprich, 1991), it is notable and problematic that several of these co-occuring psychiatric disorders (CD, Anxiety disorders) are additionally typified by impulsive and hyperactive behaviors (American Psychiatric Association, 2000).

Pre-clinical Studies

Research using both non-human primate and rodent populations are notable for the degree of control they have and their ability to more directly address some key issues revolving around the association between impulsivity and drug use. One key area that has received a fair amount of attention over the past 10-12 years has been the idea that baseline impulsivity predicts drug use severity. Animal studies, through greater control and access to baseline measures, are well suited to discern whether it is baseline impulsivity or if use severity and/or duration results in greater levels of impulsivity.

Baseline impulsivity has been shown to be predictive of later self-administration of ethanol (Poulos, Le, & Parker, 1995; Wilhelm & Mitchell, 2008) , d-amphetamine (Cardinal et al., 2000), and cocaine (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Dalley et al., 2007; Perry, Larson, German, Madden, & Carroll, 2005; Perry, Nelson, Anderson, Morgan, & Carroll, 2007; Perry, Nelson, & Carroll, 2008) in animals. These studies, which employed a variety of designs, suggest that baseline impulsive behavior is strongly implicated in the development of maladaptive substance using behaviors.

Does drug misuse result in elevated impulsivity?

Clinical studies

Cross sectional human studies, while being limited in their degree to predict behavior, have provided valuable information about the relationship between impulsivity and drug use in humans. In general, human studies comparing active drug users to non-drug using controls have shown a consistent relationship such that drug users exhibit higher levels of impulsive behaviors. This relationship has been among individuals who primarily abuse alcohol (Mitchell, Fields, D'Esposito, & Boettiger, 2005), cigarettes (Baker, Johnson, & Bickel, 2003a; Mitchell, 1999), cocaine (Coffey, Gudleski, Saladin, & Brady, 2003) and heroin (Kirby, Petry, & Bickel, 1999; Madden, Petry, Badger, & Bickel, 1997). However, these studies are unable to disentangle the direction of causality between impulsivity and substance use.

Pre-clinical Studies

Preclinical studies examining impulsivity as a function of drug use have generated mixed findings. This is due, in part, to the small number of studies in this area as well as the variability in research questions and the methodology employed to answer such questions. Among those studies examining the long-term effects of drug administration on impulsive behavior, some have some have shown clear differences in behavior as a function of drug (Roesch, Takahashi, Gugsa, Bissonette, & Schoenbaum, 2007) while others have reported less consistent findings (Perry et al., 2008).

Is impulsivity is related to a separate factor that influences drug misuse?

The idea that impulsivity is related to a separate factor that impacts susceptibility to drug misuse is the most theoretically exciting of the hypotheses presented. One possibility may be that drug use outcomes are better understood as resulting from more global regulatory difficulties where impulsivity is a symptom of a larger, more generalized set of deficits (Clark et al., 2005). In support of this idea is the repeated finding that individuals meeting criteria for a SUD commonly meet criteria for at least one pre-existing psychiatric diagnoses. While the high rates of childhood DBDs in individuals with SUDs (Biederman et al., 1991; Boyle et al., 1993; Elkins et al., 2007; Mannuzza et al., 1998; Milberger et al., 1997; Molina & Pelham, Jr., 2003; Schubiner et al., 2000) have been mentioned previously, baseline rates of the internalizing disorders of anxiety (Buckner & Schmidt, 2009; Buckner & Schmidt, 2009b; Zimmermann et al., 2003) and depression (Sihvola et al., 2008) have also been associated with later SUD status. Thus, individuals at risk for developing later SUD exhibit difficulties in both internalizing and externalizing psychological processes and such findings indicate that difficulties in regulatory behaviors may exist. Developmentally, delays in emotional, attentional, and cognitive regulatory behaviors are predictive of a number of poor outcomes (Bell & Deater-Deckard, 2007; Tarter, Kirisci, Reynolds, & Mezzich, 2004). Thus, it is not surprising that individuals at risk for later SUD have been hypothesized to exhibit a general dysregulatory trait comprised of difficulties in cognitive, emotional, and behavioral regulation (Zucker, Donovan, Masten, Mattson, & Moss, 2008; Clark, Cornelius, Kirisci, & Tarter, 2005b; Tarter et al., 2004).

Proposed Studies and Hypotheses

The series of studies that comprise this dissertation will examine the relationship between substance use and impulsive/dysregulated behavior. Study I employs animals and measures the degree to which impulsive behavior, as characterized by performance on a delay discounting paradigm for food reward, is impacted after chronic drug (heroin) administration. It is hypothesized that:

1) Animals will exhibit a pattern of performance that demonstrates a preference for the larger reward at shorter delay periods and a preference for the smaller reward when delay to the larger reward increased,

2) Heroin- but not saline-treated animals will demonstrate progressively greater locomotor activity across the drug treatment phase, demonstrating sensitization to the locomotor stimulant effects of the drug, and

3) Heroin- but not saline-treated animals will exhibit pre/post treatment differences in choice behavior across the delay intervals.

Studies II and III characterize substance use outcomes as a function of impulsive and dysregulated behaviors in a large sample of ethnically diverse, lower SES urban youth diagnosed with ADHD in childhood and a community matched control group. Specifically, Study II examines late adolescent substance use outcomes in relation to childhood conduct disorder (CD) and psychostimulant treatment in urban youth diagnosed with ADHD in childhood. It is hypothesized that:

1) Individuals diagnosed with ADHD and CD will exhibit more severe substance using behaviors when compared to individuals with ADHD without CD and to a well-matched control group, and

2) Among individuals diagnosed with ADHD in childhood, stimulant medication, regardless of duration of use and the presence/absence of comorbid CD, will not differentially impact later substance use severity and risk for SUD.

There has been a wealth of research and practice devoted to limiting the influence early expressions of impulsivity and aggression have on later outcomes (Connor et al., 2006), particularly among children with externalizing disorders, which have been shown to predict adolescent maladaptive substance use. However, few studies have examined the differential predictive utility of two distinct dimensions of externalizing behavior; aggression and delinquency. Identifying the impulsive and dysregulated behaviors, as manifested in delinquency or aggression, that predict adolescent substance use outcomes can significantly impact continued efforts in the areas of preventative and psychosocial treatments.

As such, Study III examines the degree to which childhood and adolescent ratings of aggression, delinquency and attention are differentially related to adolescent substance use outcomes in youth diagnosed ADHD. It was hypothesized that:

1) Dimensional ratings of delinquency, aggression, and problems with attention

will differentially predict adolescent substance use, and

2) Delinquency will be the most robust predictor of outcome, followed by aggression and attention, respectively.

Study I: Impulsive choice as measured in a delay discounting paradigm remains stable after chronic heroin administration.[1]

Maladaptive illicit opiate use, specifically heroin, has been associated with a number of poor outcomes (American Psychiatric Association, 2000) with long-term heroin abusers more likely to have earlier drug use onset, earlier criminal involvement, longer criminal sentences, and poorer employment histories when compared to long-term cocaine and methamphetamine users (Hser, Huang, Brecht, Li, & Evans, 2008; Hser, Evans, Huang, Brecht, & Li, 2008)

Compulsive and maladaptive drug use, in both human and animal populations has been repeatedly associated with impulsive behavior. Impulsive choice is the choice of a small immediate reward over a larger delayed reward (Evenden, 1999). In a choice paradigm where there are two possible rewards (immediate/small: large/delayed) animals repeatedly choose the reward of greater magnitude when delay to reward is equivalent between conditions. However, as delay to the larger reward increases, animals show preference for the smaller, immediately delivered reward.

Human studies comparing active drug users to non-drug using controls have shown a consistent relationship such that drug users more readily discount larger delayed rewards in favor of immediate smaller rewards. These results have been demonstrated in individuals who abuse alcohol (Petry, 2001; Vuchinich & Simpson, 1998), cigarettes (Baker, Johnson, & Bickel, 2003b; Mitchell, 1999), cocaine (Coffey et al., 2003),, and heroin (Bornovalova, Daughters, Hernandez, Richards, & Lejuez, 2005; Madden, Bickel,

[1] Harty, S.C., Whaley, J.E., Halperin, J.M, Ranaldi, R. (2011). Impulsive choice, as measured in a delay discounting paradigm, remains stable after chronic heroin administration. *Pharmacology, Biochemistry and Behavior, 98, 337-340.*

& Jacobs, 1999). As these studies are naturalistic by design, it is unclear if differences in choices are due to differences in baseline impulsivity or a result of prolonged and sustained substance use.

Animal studies have shown that differences in baseline impulsivity are associated with later self-administration of ethanol (Poulos et al., 1995; Wilhelm & Mitchell, 2008), d-amphetamine (Cardinal et al., 2000), and cocaine (Belin et al., 2008; Dalley et al., 2007; Perry et al., 2005; Perry et al., 2007; Perry et al.,2008). However, there are relatively few studies examining impulsive choice as a function of drug taking and these studies have generated mixed findings. Paine et al. (2003) reported a transient increase in impulsive choice as a result of cocaine administration in animals previously trained on a delay discounting paradigm. Richards et al. (1999) found that animals decreased impulsive responding when administered acute, non-behaviorally disruptive doses of amphetamine (0.5, 1.0, 2.0 mg/kg) and exhibited increased impulsivity when the dose was larger (4.0 mg/kg) but administered 22 hours before the test session.

Some studies that examined the long-term effects of chronic cocaine administration on impulsive choice found that animals previously exposed to cocaine were significantly more impulsive up to 3 months after drug exposure (Simon, Mendez, & Setlow, 2007; Roesch et al., 2007), suggesting that prolonged exposure to large amounts of cocaine results in long-term neural and behavioral adaptations. However, Stanis et al. (2008) showed that while animals receiving 20 days of amphetamine exhibited immediate and long-term locomotor sensitization, they did not display differences in delay discounting when compared to saline-treated animals.

The objective of this study was to measure alterations in impulsive choice behavior, measured through a delay discounting paradigm, as a function of chronic heroin administration. To our knowledge, this is the first study to examine impulsive choice as a function of chronic heroin administration

Methods

The protocols used in the present experiments were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the Queens College Institutional Animal Care and Use Committee.

Animals

Subjects consisted of 25 male Long Evans rats, facility-bred, individually housed and maintained on a 12 h light: 12 h dark cycle (lights off 0600). All animals had unlimited access to food until the experimental sessions started, at which time access to food was restricted to daily rations that maintained their weights at 85% of their free-feeding values.

Testing Apparatus

Operant chambers

Instrumental conditioning and delay-discounting sessions were conducted in operant conditioning chambers measuring 30 x 22 x 27 cm (*l* x *w* x *h*). One wall was equipped with two retractable levers with white stimulus lights above each lever, and a food trough between levers. Each chamber was housed in a ventilated, sound-attenuating box.

Activity monitors

Locomotor activity tests were conducted in activity chambers measuring 40.5 x 20.5 x 24.5 cm (*l* x *w* x *h*). Each chamber was equipped with eight photo-emitters positioned along the length of the chamber 6 cm above the floor, each paired directly opposite a photocell.

Procedure

Training:

The delay discounting paradigm used in this study was adapted from Evenden and Ryan (1996). Animals were trained to press a lever on a continuous reinforcement schedule where each lever press resulted in the delivery of one food pellet. Sessions lasted 20 minutes with the right and left levers introduced on alternate days. Training continued until animals lever pressed for 100 pellets on two consecutive days.

After lever training, animals were run through a series of 3 delay discounting sessions. Each session contained 5 blocks of trials that were 100 s in duration. Blocks contained 8 trials; 2 forced choice followed by 6 free choice trials. At the onset of the forced choice trial, the right or left lever was randomly introduced and the accompanying light was illuminated. Pressing the left lever resulted in the delivery of a small (1 food pellet) immediate reward. Pressing the right lever resulted in the delivery of a large (5 pellets) delayed reward. During free choice trials, both levers were introduced. After a response or 30 seconds, levers were retracted and the light was extinguished for the remainder of the trial. Sessions consisted of the following ascending delay sequences: 0, 2, 4, 8, 16 s followed by 0, 5, 10, 20, 40 s, and 0, 10, 20, 40, 60 s. Animals experienced each sequence for a minimum of 7 days and until they exhibited a 3-day average rate of 80% delay lever choice at the 0 second condition. Training was completed when animals exhibited a pattern of performance on the terminal sequence (0, 10, 20, 40, 60) such that large reward lever responses were reliably below 50% on the larger delay choices. Such performance allowed for the calculation of an indifference point (IP), operationalized as the delay value where the likelihood of responding to either the large or small reward lever was equal. Responding was considered stable when animals exhibited a similar pattern of performance over a period of three consecutive days such that there was a significant difference in delayed reward choices across the 5 blocks of trials.

Experimental Phase

After animals completed training they were randomly assigned to either saline or heroin groups and placed in locomotor activity chambers for 30-min sessions for 12 consecutive days. Animals received intraperiotneal injections of saline for 3 days (habituation) and then received either heroin or saline for the following 9 days (treatment) immediately prior to placement in the activity chambers. Three days following the last injection and activity test, animals were again placed daily in operant chambers where they experienced the terminal delay sequence (0, 10, 20, 40, 60) and their IPs were reassessed.

Drug and doses

All solutions were prepared prior to the onset of the experiment. Heroin (NIDA, Bethesda, MD) was dissolved in saline to achieve a concentration of 2 mg/ml. Solutions were injected in 1 ml/kg volumes.

Data Analysis

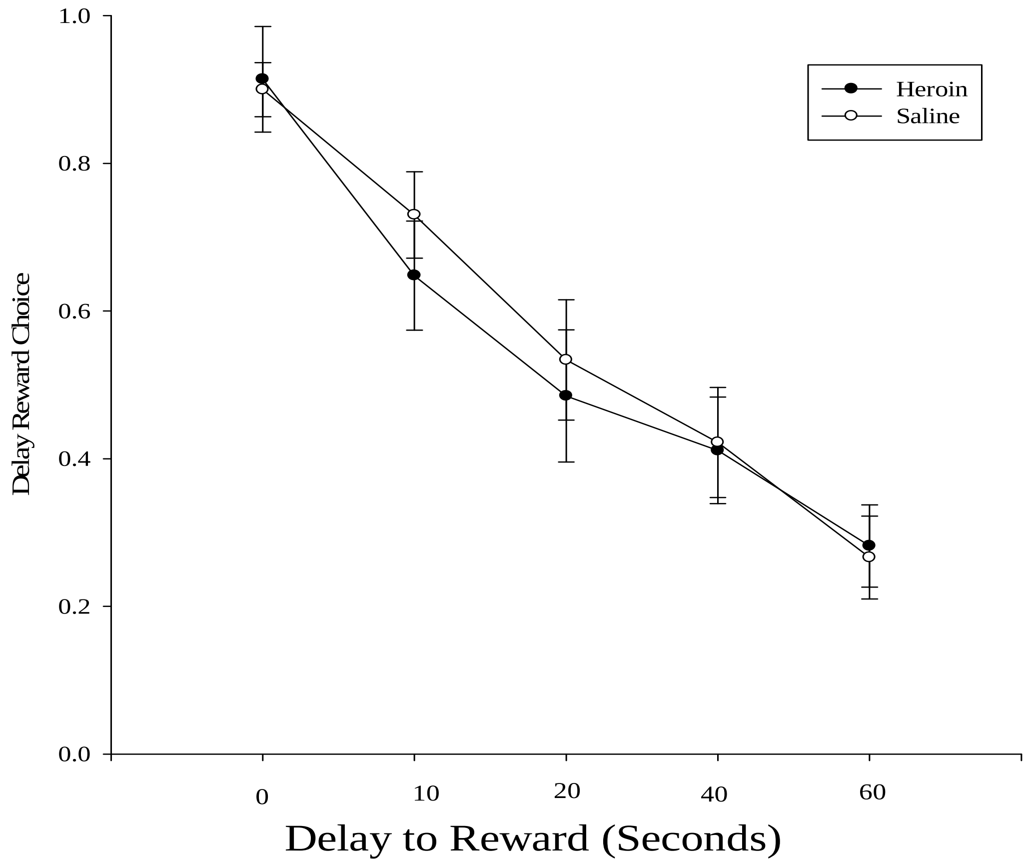
Independent samples t-tests were used to assess group differences. In order to assess differences in performance across the delay intervals (0, 10, 20, 40, 60), a 2x5 (group x delay) mixed factorial analysis of variance (ANOVA) was preformed on the performance data when animals met criteria for training and at the completion of the study. A 2x2 mixed factorial design was employed to assess for differences as a function of group (between-subjects) across the before and after IP sessions (within-subjects).

Locomotor tests evaluated the total locomotor beam breaks per 30-minute session. Only the data from 9 treatment sessions were analyzed, as habituation sessions (days 1 to 3) did not differ between groups. A 2x9 mixed factorial ANOVA was employed to assess group differences in locomotor activity as a function of group (between-subjects) and session (within-subjects).

Results

There were no differences between heroin and saline groups in weight at baseline [$t(1,23) = .21$, $p = .84$] or days to complete the training phase [$t(1, 23) = 1.47$, $p = .15$]. Before the treatment phase both the heroin and saline groups showed decreases in the likelihood of choosing the large reward as the delay to the large reward increased [see Figure 1A; $F(4, 20) =.44$, $p = .78$] and showed similar IPs [see Figure 1B; $t(1,23) = .28$, $p = .78$] .

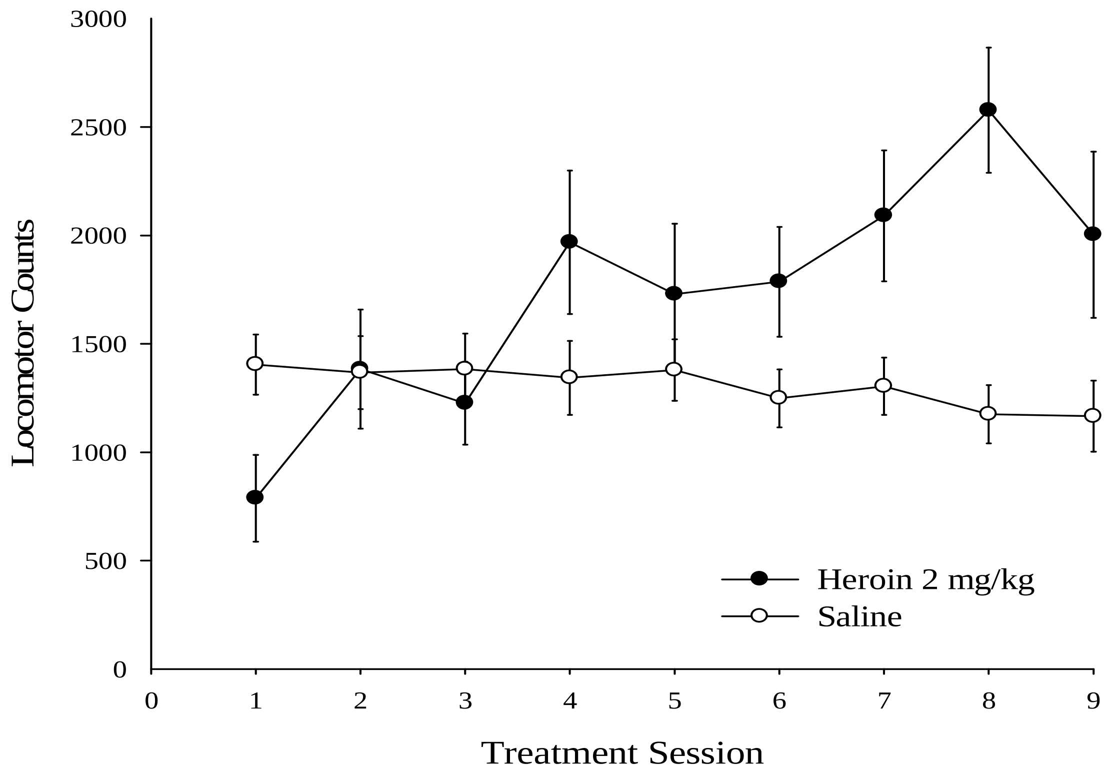
Figure 1
A.) Mean (+/- SEM) proportions of large reward choices at baseline as a function of delay interval.



B: Mean indifference points (seconds) as a function of chronic heroin or saline treatment

During the treatment phase heroin- but not saline-treated, animals demonstrated progressively larger increases in activity across the nine treatment sessions (see Figure 2). Results of the mixed-design two-way ANOVA revealed a significant session by group interaction [$F(8,16) = 6.62$, $p \leq .001$]. Tests of simple main effects revealed a significant session effect for the heroin group [$F(8,7) = 8.80$, $p = .005$].

Figure 2: Mean (+/- SEM) locomotor counts (beam breaks) per session in groups receiving chronic heroin or saline injections (IP) immediately prior to each session.

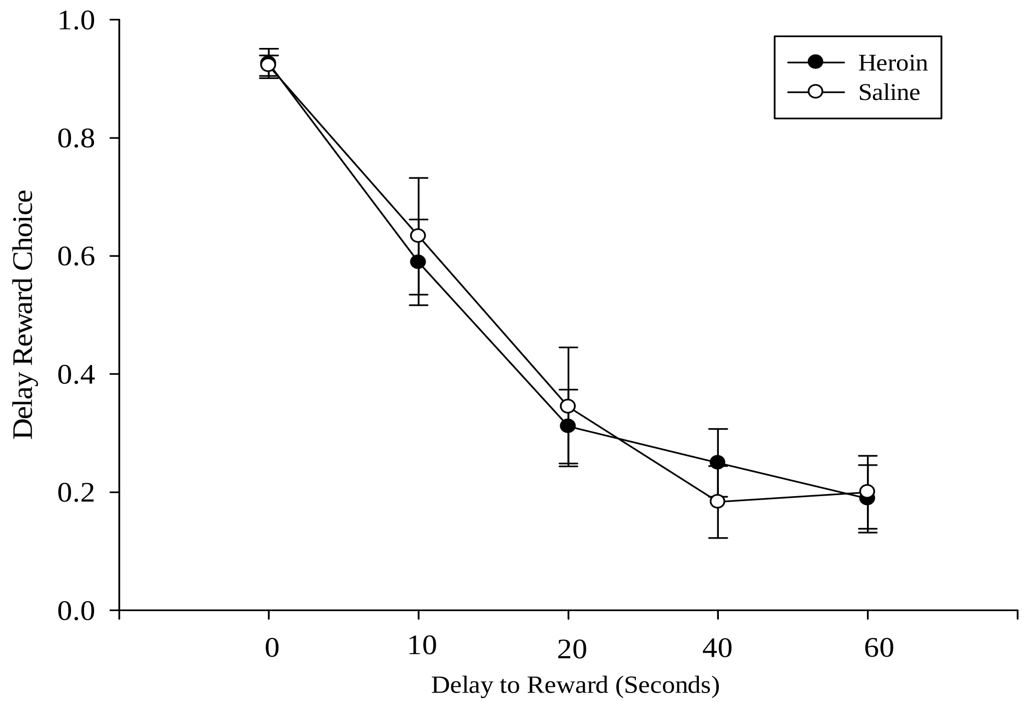


After the treatment phase, tests examining large reward lever presses revealed a significant difference in performance as a function delay [$F(4, 20) = 83.35$, $p < .01$], but not group [$F(4, 20) = .87$, $p = .50$] (see Figure 3A). Saline- and heroin-treated animals generated similar IPs after the treatment phase [$t(1,23) = .26$, $p = .76$] (see Figure 3B).

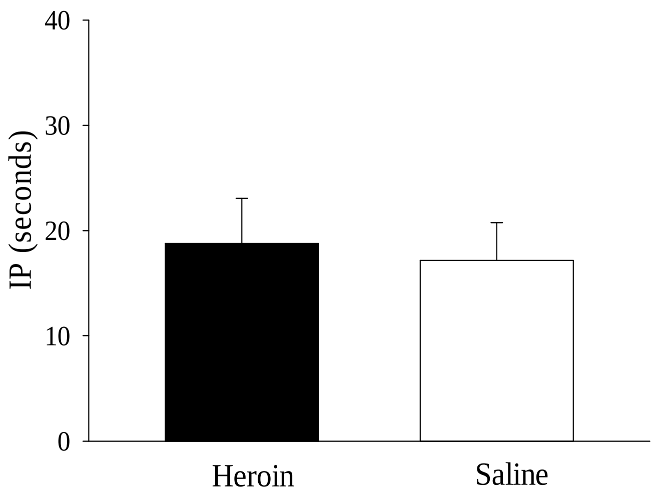
The mixed-design 2 x 2 ANOVA examining group differences across before and after treatment phases revealed significant differences in IP as a function of treatment (before-after),[$F(1,23) = 6.98$, $p = .02$], such that, regardless of group, animals exhibited greater impulsive choice in the test after treatment (compare Figure 3B to Figure 1B).

Figure 3

A: Mean (+/- SEM) proportions of large reward choices as a function of delay interval and treatment.



B: Mean indifference points (seconds) as a function of chronic heroin or saline treatment



Discussion

This experiment examined the effects of chronic heroin administration on a measure of impulsive choice. Animals exhibited a preference for the larger reward at shorter delay periods and a preference for the smaller reward when delay to the larger reward increased. Heroin- but not saline-treated animals demonstrated progressively greater locomotor activity across the 9-day treatment phase, demonstrating sensitization to the locomotor stimulant effects of the drug. After the treatment phase, animals were again placed in the delay discounting paradigm and IPs were reassessed. Similar to performance before treatment, heroin and saline treated animals did not demonstrate differences in choice behavior across the delay intervals or as measured by the IP. Notably, both groups were more impulsive post-treatment relative to their baseline IP assessments. It may be that the increased impulsivity seen post-treatment was a result of learning. Additionally, it may be that the administration procedure, regardless of substance, resulted in a change in behavior

Currently, there are only a handful of experiments examining impulsive choice as a function of drug administration and, to our knowledge, this is the first study to examine delay discounting as a function of chronic heroin and sensitization. The primary results of this study indicate that prolonged heroin administration, resulting in sensitization of the locomotor response, does not impact choice behavior as measured by a delay discounting paradigm. The lack of an effect among heroin-treated animals adds to a small literature (Stanis et al., 2008; Winstanley et al., 2007), that indicates that drug use per se does not contribute to increased impulsive choice.

We chose to administer to the animals a dose (2mg/kg) of heroin that has been shown to result in locomotor sensitization (Ranaldi et al., 2009) and opiate sensitization is associated with long-lasting changes in brain reward systems, namely the dopamine mesolimbic system (Kalivas & Duffy, 1987; Nestby et al., 1997; Spanagel & Shippenberg, 1993; Vanderschuren & Kalivas, 2000). It is unlikely that the current treatment regimen did not produce neuroadaptations in the mesolimbic system. This suggests that whatever aspects of the mesolimbic dopamine system are modified by chronic heroin, they may not be involved in impulsive behavior. However, further research is needed before making more definitive conclusions in this regard.

Taken together, the results of this study do not support the hypothesis that chronic heroin administration results in sustained changes to the processes governing choice behavior. As there are currently only a few existing studies examining the role of chronic drug administration on later impulsive choice, and that these studies have generated dissimilar findings, this study helps to further clarify the impact drug use has on impulsive behaviors, such as impulsive choice. Further, a recent study by McNamara et al. (2010) reported that baseline differences in inhibitory control do not predict differences in heroin self-administration. Such findings, in combination with those of the current study, suggest that impulsivity may have little to do with heroin abuse.

Our results must be interpreted within the limitations of the study. We measured impulsivity using a delay discounting paradigm where impulsivity was operationalized as the calculated delay to large reward at which the animal shows equal likelihood of choosing the delayed large reward or the immediate small reward (IP). However, impulsivity is a heterogeneous construct (Evenden, 1999) and it is possible animals might exhibit differences on another measure of impulsivity. Additionally, animals received intraperiotneal injections of either heroin or saline. There is evidence to suggest that the mode of administration may differentially impact the degree to which drugs affect the neural systems involved in reward-related behavior (Setlow, Mendez, Mitchell, & Simon, 2009). It is possible that animals would have performed differently if allowed to self-administer drug.

The limitations listed above are addressed, in part, by a study (Dalley et al., 2005) that also examined the relation between impulsivity and chronic heroin. They operationalized impulsivity as reduced inhibitory control, defined as the frequency of premature responses on a 5-choice serial reaction time task. Additionally, chronic heroin was self-administered as opposed to experimenter-administered as in the present experiment. Similar to the findings generated in the current study, the Dalley et al. (2005) study showed no effect of heroin self-administration on a measure of impulsivity.

Conclusion

Chronic heroin administration, resulting in a sensitized locomotor response, does not increase impulsive choice for food reward as measured in a delay discounting paradigm in rats. If such findings generalize to other measures of impulsivity and to human behavior, they would suggest that impulsive characteristics commonly observed in heroin abusers are not secondary to brain changes associated with substance use.

Study II: The impact of Conduct Disorder and stimulant medication on later substance use in an ethnically diverse sample of individuals diagnosed with ADHD in childhood.[2]

Longitudinal studies indicate that individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD) in childhood have poorer outcomes in educational (Mannuzza, Klein, Bessler, Malloy, & Hynes, 1997), cognitive (Fischer, Barkley, Edelbrock, & Smallish, 1990), and social (Lambert, Hartsough, Sassone, & Sandoval, 1987; Taylor, Chadwick, Heptinstall, & Danckaerts, 1996) functioning when compared to age matched controls. A diagnosis of ADHD in childhood is additionally associated with elevated rates of substance use and substance use disorders (SUDs) during adolescence and young adulthood (Mannuzza et al., 1998; Schubiner et al., 2000a; Elkins et al., 2007a; Milberger et al., 1997). The subsequent development of substance use in individuals with ADHD has been found to be largely impacted by the presence of comorbid conduct disorder (CD), (Barkley et al., 1990; Molina & Pelham, Jr., 2003; Molina et al., 2002). However, several studies have shown an association between ADHD and increased substance use over and above the risk posed by CD (Burke, Loeber, & Lahey, 2001; Elkins et al., 2007; Milberger et al., 1997) whereas others have suggested that CD mediates the relationship between ADHD and later substance misuse (Brook et al 2010). Thus, it may be that ADHD and CD together generate a greater risk for later substance misuse than either disorder alone (Flory & Lynam, 2003).

---

[2] Harty, S.C., Ivanov, I., Newcorn, J.H. Halperin, J.M. (In Press). The impact of Conduct Disorder and stimulant medication on later substance use in an ethnically diverse sample of individuals diagnosed with ADHD in childhood. *Journal of Child and Adolescent Psychopharmacology.*

Another issue of considerable importance is whether treatment of ADHD with stimulant medication impacts the development of substance use and SUDs, as stimulants are controlled substances with high potential for abuse. Pre clinical studies examining the vulnerability to addiction as a function of prior exposure to methylphenidate (MPH) have generated mixed findings. Some studies have shown that early exposure to MPH enhances later drug taking (Brandon et al 2001; Valvassori et al 2007; Wooters et al 2006) while others have found that early exposure to MPH results in a decrease in the rewarding effects of drug (Andersen, Arvanitogiannis, Pliakas, LeBlanc, & Carlezon, Jr., 2002; Carlezon, Jr., Mague, & Andersen, 2003; Mague, Andersen, & Carlezon, Jr., 2005). In addition, these studies include important differences in dose amounts, age at first exposure, and timing of stimulant exposure; variables that may moderate the relationship between early exposure to MPH and later outcome (Wooters et al 2006). In youth with ADHD, most studies report no effect of early stimulant treatment on substance use outcomes, but there are conflicting findings.

To date, only one longitudinal study in humans has reported a positive relationship between stimulant treatment in childhood and later substance use. Lambert and Hartsough (1998) divided an ethnically-diverse sample of children with ADHD from largely lower socioeconomic strata into 3 medication groups; those never prescribed stimulant medication, those receiving medication for less than 1 year, and those with more than 1 year of medication treatment. Children treated with stimulants in childhood had significantly higher rates of daily smoking and cocaine dependence in adulthood. In contrast, two studies have suggested a protective effect of psychostimulant treatment, such that medicated individuals exhibited reduced SUD rates when compared to those with ADHD not receiving such treatment (Biederman, Wilens, Mick, Spencer, & Faraone, 1999; Loney, Kramer, & Salisbury, 2002). The largest number of studies have found that childhood psychostimulant treatment does not significantly influence the likelihood of pre-adolescent (Chilcoat & Breslau, 1999; Molina et al., 2007) or adolescent/young adult (Barkley, Fischer, Smallish, & Fletcher, 2003; Biederman et al., 2008; Mannuzza et al., 2008) SUD in either direction.

As shown in Table 1, the majority of findings indicate that psychostimulant treatment of ADHD does not increase risk for later SUDs. However, the variability in findings suggests that some key issues remain unresolved, perhaps due in part to the fact that naturalistic longitudinal studies, by their very nature, are uncontrolled. As such, a number of factors exist both within and across studies that can potentially account for the diverse findings. For example, the only study that reported a negative influence of psychostimulant treatment was also one of only two studies to include an ethnically-diverse sample from lower socioeconomic strata, and socioeconomic and ethnic differences have been shown to clearly impact substance use trajectories (Anglin, Booth, Ryan, & Hser, 1988; Anglin, Ryan, Booth, & Hser, 1988; Gilman et al., 2008; Gilman et al., 2008). However, this study also failed to adequately address issues pertaining to diagnostic severity and comorbidity. Other studies either excluded children with CD from their initial childhood sample (Mannuzza et al., 1998) or had large differences in the rate of CD between the treated and untreated groups (Barkley et al., 2003; Biederman et al., 1999). That latter circumstance can introduce important differences in baseline risk unrelated to medication status that are not easily controlled for statistically (Miller & Chapman, 2001).

Table 1
Summary of longitudinal studies examining the effect of stimulant medication on later substance use in individuals diagnosed with ADHD

Author	ADHD Sample size At follow up	Developmental stage at Follow-Up	Primary Ethnicity	Outcome
Lambert and Hartsough (1998)	174	Young Adulthood	77% Caucasian	↑
Biederman et al (1999)	75	Late Adolescent	Caucasian	↓
Loney et al (2002)	219	Young Adulthood	98% Caucasian	↓
Chilcoat and Breslau (1999)	146	Early Adolescence	46% African American	↔
Molina et al (2007)	486	Early Adolescence	61% Caucasian	↔
Barkley et al (2003)	147	Young Adulthood	94% Caucasian	↔
Biederman (2008)	112	Young Adulthood	Caucasian	↔
Mannuzza et al (2008)	176	Young Adulthood	Caucasian	↔

Note: Early Adolescence = 11-13, Late Adolescent = 15-18, Young Adulthood = 21-25
↑ = Psychostimulant medication increased risk for later substance use
↓ = Psychostimulant medication decreased risk for later substance use
↔ = Psychostimulant medication did not significantly impact risk for later substance use

This prospective 10-year follow-up study examining substance use outcomes in a sample of primarily non-white children from lower socioeconomic backgrounds diagnosed with ADHD in childhood had two primary aims: 1) to compare individuals diagnosed with ADHD, with and without childhood CD, to a well-matched control group on late adolescent substance use outcomes and 2) to examine, among individuals diagnosed with ADHD in childhood, the degree to which stimulant medication differentially affects later substance use severity and risk for SUD. Notably, this sample was highly variable with regard to the duration of treatment (none – 12 years), allowing for a detailed investigation of duration-related effects in a sample where treatment duration was unrelated to ADHD severity or the presence of CD in childhood.

Methods and Materials

Participants

Ninety-seven adolescents/young adults who were evaluated in a research protocol during childhood (mean age at baseline = 9.05 years, *SD* = 1.28), were seen for follow-up on average 9.30 (*SD* = 1.65) years later. They were drawn from a group of 169 youth who were recruited between 1990 and 1997 for a study of ADHD and aggression. Of these 169 participants, 18 refused to participate in the follow-up, two were known to be deceased, seven were incarcerated, and 46 were lost to follow-up. We attempted to locate missing participants by contacting known family members and via information publicly available on the internet. However, this sample was drawn from a highly mobile inner-city population and many individuals could not be found. Nevertheless, those who were and were not assessed at follow-up did not differ significantly with regard to age at initial evaluation, rates of childhood comorbid diagnoses, Full Scale IQ, socio-economic status (SES), or ADHD and other disruptive behavior disorder ratings at initial assessment (all $p > .10$). Thus, although a substantial number of the original sample was lost to follow-up, the sub-sample that participated in the follow-up study appears to be representative of the larger group.

At baseline (ages 7 – 11 years), participants were evaluated using parent report on the Diagnostic Interview Schedule for Children (DISC). Parent and teacher reports using the Child Behavior Checklist and IOWA Conners Rating Scale, respectively, were also obtained. To insure cross-situationality of ADHD symptoms, children were required to have teacher ratings on the inattention/overactivity scale of the IOWA greater than 1.5 SD above the mean for age and gender. Based upon this evaluation, 32 (33%) children met criteria for CD in addition to ADHD. As shown in Table 2, individuals diagnosed with ADHD+CD in childhood had significantly higher rates of psychiatric comorbidity, and higher parent ratings of externalizing, but not internalizing or attention problems, compared to those with ADHD but not CD in childhood. Teachers rated those with CD higher on both subscales of the IOWA Conners.

Table 2

Childhood characteristics as a function of presence/absence of CD

	ADHD			ADHD + CD			
	(*n* = 66)			(*n* = 32)			
Measure	Mean	SD		Mean	SD	*t*	*p*
Age	9.04	1.36		9.18	1.17	.47	.64
SES	38.21	19.03		31.81	14.10	1.75	.09
WISC FSIQ	95.47	14.19		90.73	14.29	1.51	.22
CBCL							
Attention problems	71.25	9.95		74.30	10.14	1.33	.19
Externalizing	66.06	10.66		78.22	7.32	3.22	.03
Internalizing	63.97	12.30		67.81	11.07	2.16	.10
IOWA Conners							
I/O	10.67	3.27		12.40	2.75	2.51	.01
A/D	7.14	4.81		10.30	3.80	3.15	<.01
DISC						X^2	*p*
% ANX	22.72			50.00		7.41	.01
% MOOD	6.06			18.75		3.79	.05

Note: WISC-R/III = Wechsler Intelligence Scale for Children, Revised/3rd Ed; CBCL = Child Behavior Checklist; DISC = Diagnostic Interview Schedule for Children

Eighty five never-ADHD controls were recruited during late adolescence/early adulthood from the same urban communities as the ADHD group. Most were identified via targeted advertisements in neighborhoods that matched the ADHD sample by zip code. Controls resembled probands on most important demographic variables including age, gender, ethnicity, SES, and general intellectual functioning (all $p > .05$), but did not have a history of ADHD in childhood or adolescence as ascertained using the DISC ADHD module during a screening interview. Prospective controls were excluded if they had any chronic medical or neurological condition, schizophrenia, a pervasive developmental disorder, or a Full Scale IQ score below 70, as was the case for the original ADHD sample.

At follow-up, both ADHD groups exhibited higher levels of parent-rated internalizing and externalizing than Controls, and the ADHD+CD group displayed higher parent ratings of externalizing and internalizing problems relative to the ADHD only group. The two ADHD groups did not differ in parent-rated attention problems although, as expected, they were both greater than Controls (see Table 3). Although the ADHD and ADHD+CD groups did not differ significantly in IQ at baseline, follow-up IQ scores for the ADHD+CD group were significantly lower when compared to both the ADHD group and Controls.

Table 3
Late adolescent characteristics as a function of childhood CD

	Control		ADHD		ADHD + CD			
	(n = 85)		(*n* = 66)		(*n* = 32)			
Measure	Mean	SD	Mean	SD	Mean	SD	*F*	*p*
Age	18.51	1.68	18.23	1.64	18.83	2.01	1.33	.27
SES	40.66	16.75	45.97	19.62	37.53	12.26	2.94	.06
*WAIS-FSIQ	96.79	15.33	96.13	15.25	87.03	12.29	4.97	.01
CBCL								
**Attention	51.52	2.89	60.54	9.77	63.39	11.52	33.62	<.01
***Internalizing	47.97	9.89	54.90	13.42	60.79	12.53	14.49	<.01
***Externalizing	48.35	10.47	57.97	13.03	66.75	10.85	30.28	<.01
							T	*p*
Treatment Duration in years			2.95	3.60	3.21	3.37	.34	.73

Note: WAIS = Wechsler Adult Intelligence Scale 3rd Ed; CBCL = Child Behavior Checklist
*The ADHD+CD group was significantly different from Control and ADHD groups
**Both ADHD groups were significantly different from Controls
***All three groups differed significantly

This late adolescent sample was predominately male (87.8%) and racially and ethnically diverse (26.0% African-American, 23.8% Caucasian, 35.4% Hispanic, and 14.4% mixed or other ancestry). Ages generally ranged from 16 to 22 years, however two individuals diagnosed with ADHD had follow-up ages of 25 and 26, and one was 15. Mean socioeconomic status, estimated from parental occupation and education using the socioeconomic prestige scale (Nako K & & Treas, 1994), was 42.57 (*SD* = 17.34). The sample comprised individuals with the full range of scores on this measure (20 – 96); but the modal score was 20 (n = 32, 17.7%), representing, on average, a low to lower-middle status group, with a substantial portion at the poverty level.

Participants and their parents were proficient in English, and were compensated for their time and travel. All procedures were approved by the Institutional Review

Boards of the participating institutions. Written informed consent was obtained from all adolescents above the age of 18 years and the parents of those under the age of 18 years. Assent was obtained from youth under 18 years-old.

Medication Status

At follow-up, treatment history was obtained through administration of a "Services Received Interview" where parents detailed participant exposure to psychosocial interventions and/or pharmacotherapy. Participants were specifically queried regarding duration, type, and age at which treatment occurred. Supplemental information was provided through the initial interview portion of the Kiddie-SADS Present and Lifetime Version (Kaufman et al., 1997) and a review of records from the initial assessment, which included information regarding childhood medication status and history. Using all available data, 69 (71%) individuals in the ADHD group had received some treatment with psychostimulants (Mean duration = 4.26 years; SD = 3.48; Range = 1 or 2 doses to 12.00 years); 28 never received medication treatment. Additionally, 23 (24%) individuals diagnosed with ADHD received a pharmacologic intervention other than psychostimulants. Due to the high variability in treatment duration, it seemed problematic to only combine those with treatment into a single group. Therefore, we separated individuals into four independent groups of approximately equal size: individuals with no history of stimulant medication (n= 28), those who were treated for up to one year (n = 19, Mean = .49 years, SD = .24; range = .25 – 1.00), one to five years (n = 28, Mean = 3.36 years, SD = 1.05; range = 1.5 – 5.0), and those who were treated for greater than five years (n = 22, Mean = 8.67 years, SD = 1.86; range = 5.25 – 12.0).

As shown in Table 4, comparison of treatment groups at baseline revealed that groups were generally similar with regard to parent and teacher ratings of behavior and patterns of comorbidity. However, individuals receiving medication for 1-5 years had significantly higher teacher rated inattention/overactivity compared to those receiving up to 1 year of medication, and individuals receiving treatment for up to 1 year had higher parent ratings of Internalizing problems when compared to those receiving medication for greater than 5 years. As shown in Table 5, analyses examining group differences among the medication group on follow-up measures of age, SES, and intellectual and psychological functioning revealed that individuals receiving treatment for up to one year had significantly higher Externalizing scores when compared to individuals never receiving medication treatment. Otherwise, groups did not differ on any other follow-up measure.

Table 4
Childhood characteristics of medication subgroups

	None		One or less		1 - 5		Greater than 5			
	(*n* = 28)		(*n* = 19)		(n = 28)		(*n* =22)			
Measure	Mean	*SD*	Mean	SD	Mean	SD	Mean	SD	*F*	*P*
*Age	9.44	1.56	9.51	1.41	8.81	1.16	8.53	1.31	3.38	.02
SES	32.19	16.50	37.78	17.59	34.52	14.97	43.73	21.50	1.78	.16
WISC- FSIQ	89.07	14.02	93.55	*11.49*	96.74	13.82	97.10	16.65	1.76	.16
IOWA Conners										
**I/O	10.39	3.18	9.61	3.98	12.73	2.22	11.23	2.88	4.69	.004
A/D	7.19	4.59	9.61	4.73	9.19	4.61	7.05	4.84	1.78	.16
CBCL										
Attention problems	71.00	10.84	72.00	10.68	75.16	9.43	70.25	9.22	1.10	.36
Externalizing	67.07	11.38	71.67	10.32	73.00	9.64	67.05	13.14	1.79	.16
***Internalizing	64.00	13.24	70.00	10.45	67.28	10.25	59.30	12.11	3.07	.03
DISC									X^2	*p*
% CD	32.14		21.05		35.71		36.36		1.42	.70
% ANX	35.71		47.37		21.43		27.27		3.91	.27
% MOOD	10.71		10.53		10.71		9.09		0.05	.99
% Receiving Other Pharmacologic Treatment	10.71		26.32		25.00		36.36		6.08	.11

Note: WISC-R/III = Wechsler Intelligence Scale for Children, Revised/3rd Ed; CBCL = Child Behavior Checklist; DISC = Diagnostic Interview Schedule for Children; CD = Conduct Disorder, ANX, = any anxiety disorder; MOOD = any mood disorder.

*Post hoc tests did not reveal any significant individual group differences
** Individuals receiving medication for 1-5 years were significantly different than those receiving up to 1 year of medication
*** Individuals receiving treatment for up to 1 year were significantly different than those receiving medication greater than 5 years.

Table 5

Follow-up characteristics of medication subgroups

	None		One or Less		1-5		Greater than 5			
	(*n* = 28)		(*n* = 19)		(*n* = 28)		(*n* = 22)			
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*p*
Age	18.45	2.05	18.75	2.30	18.51	1.34	17.99	1.44	.65	.59
SES	39.59	18.36	41.44	14.68	44.52	17.65	47.86	20.36	.94	.43
WAIS-FSIQ	89.86	10.09	90.00	13.74	95.52	15.10	97.32	19.56	1.51	.22
CBCL										
*Externalizing	55.36	12.75	66.53	12.04	63.74	11.83	59.05	13.69	3.22	.03
Internalizing	53.00	13.42	63.67	12.73	57.67	13.92	55.57	11.99	2.16	.10

Note: WAIS = Wechsler Adult Intelligence Scale, 3rd Ed; FSIQ = Full Scale IQ; CBCL = Child Behavior Checklist
* Tukey's Post Hoc Test revealed a significant difference between those that never received medication treatment and those receiving treatment for up to one year

Substance Use Status

Determinations of substance use behaviors and SUD status were obtained using the Kiddie-SADS –PL, which was administered at follow-up to each adolescent, and separately to each participant's parent. SUDs were separated into disorders resulting from alcohol (ETOH) and illicit drug (DRUG) misuse. Evaluators were Ph.D. level psychologists or trained psychology graduate students blind to group membership. Responses were combined across interviewee by item; if either informant indicated that the item caused significant distress or impairment, the symptom was judged to be present. Diagnoses of alcohol and drug abuse and dependence, past and present, were collapsed into binary (yes/no) categories that combined diagnoses of abuse and dependence.

Severity of substance use was assessed using the Rutger's Alcohol and Drug Use Questionnaire (Labouvie, Bates, & Pandina, 1997a). Adolescents were asked to report use of cigarettes, alcohol, marijuana, and "other drugs" (cocaine, stimulants, psychedelics, heroin, analgesics, sedatives, club drugs, and non-prescription drugs) over the past 3 years. These latter categories were combined into one group because of generally low rates of use for any individual substance. The Rutger's substance use screening measure asks adolescents about the frequency (how often) and intensity (amount) of substance use. For example, at the beginning of the cigarette use module participants were asked if they had smoked a whole cigarette at least one time during the preceding 3 years. If they indicated that they had smoked during that time they were asked to indicate the frequency (1-2 times, 3-9 times….1000 or more times) and intensity of their use when they smoked (less than 1 a day, 1-4 cigarettes...More than 2 packs). Similar to Labouvie et al. (1997), severity of substance use was defined as the product of frequency x intensity of use, resulting in a unitary dimensional measure of substance use severity for each drug class. The four severity variables (3-year cigarette, alcohol. marijuana, and other use) were square root transformed to normalize their distributions.

Statistical Analysis

Substance use outcomes as a function of Childhood CD:

A one-way multiple analysis of variance (MANOVA) was used to assess differences between the ADHD+CD, ADHD and Control groups on square-root transformed measures of 3-year substance use severity outcomes for tobacco, alcohol, marijuana, and other drug use. Following a significant Wilks' Lambda, one-way ANOVAs were conducted to determine which measures significantly distinguished the groups followed by post-hoc Tukey HSD to determine specific group differences. To evaluate categorical SUD outcomes, binary logistic regression analyses were conducted using the Control group as the indicator to which the ADHD+CD and ADHD groups were compared.

Relation of substance use severity and SUD to stimulant medication treatment:

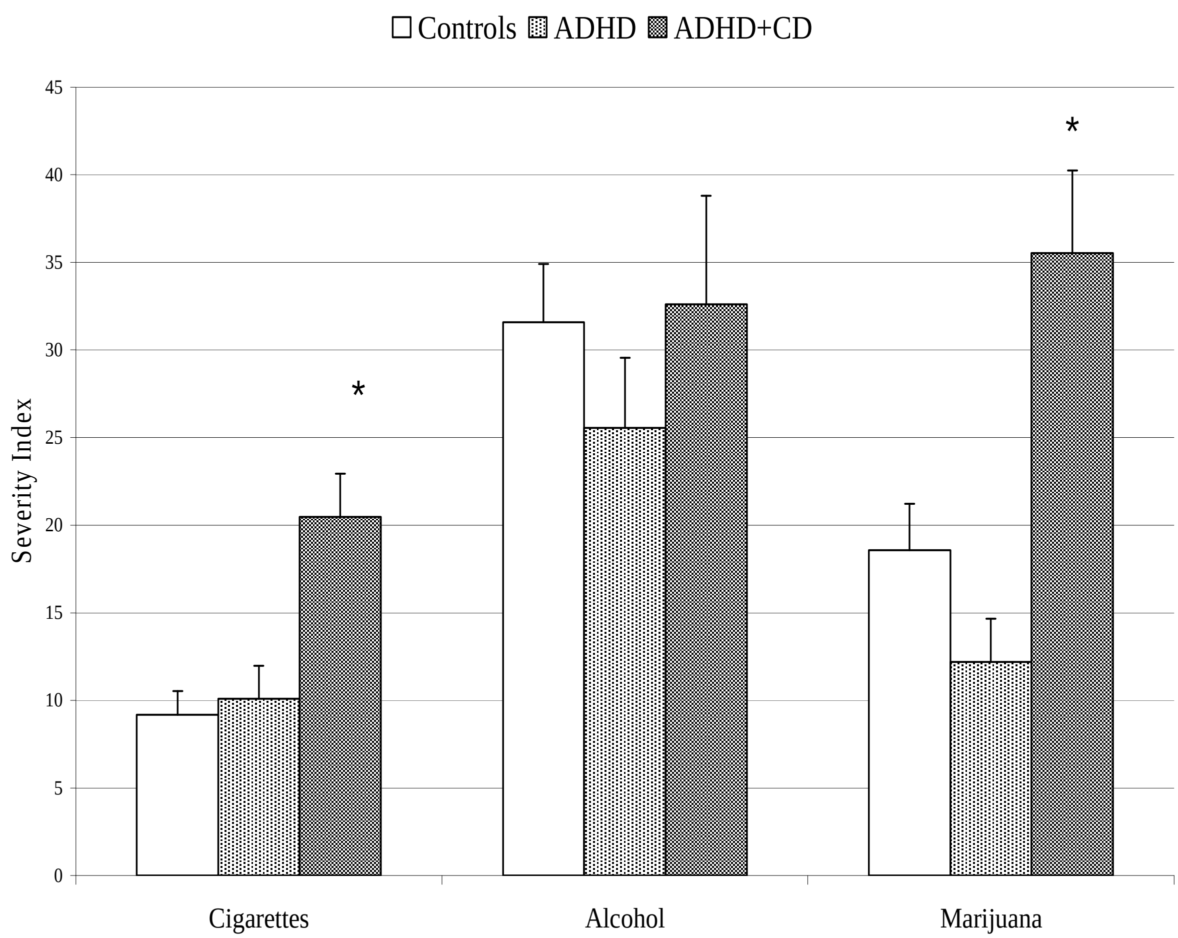
Among those individuals diagnosed with ADHD in childhood, a MANOVA and Chi square tests were used to examine the relationship between medication treatment group and late adolescent substance use severity and SUD status, respectively. Previous longitudinal studies have used childhood CD and other indicators of clinical severity in an attempt to control for pre-existing differences between treated and untreated groups; however, as seen in Table 4, our groups did not differ on these measures at baseline.

Results

As shown in Figure 4, the one-way MANOVA examining the differences between the ADHD+CD, ADHD and Control groups on measures of 3-year substance use severity revealed a significant effect among groups, allowing for the further examination of individual ANOVAs ($\lambda = .84$, $p \leq .001$, $\eta p2 = .082$). Results of the one-way ANOVAs examining late adolescent substance use severity revealed significant differences among measures of 3-year cigarette, $F(2,177) = 7.92$, $p = .001$, and marijuana, $F(2, 177) = 10.58$, $p < .001$ use. Post hoc tests revealed that the ADHD+CD group had significantly higher rates of 3-year cigarette and marijuana use severity when compared to both the Control and ADHD groups (all $p < .01$). The ADHD and Control groups did not differ on either measure.

Figure 4

Childhood Conduct Disorder predicts 3-year severity of cigarette and marijuana use



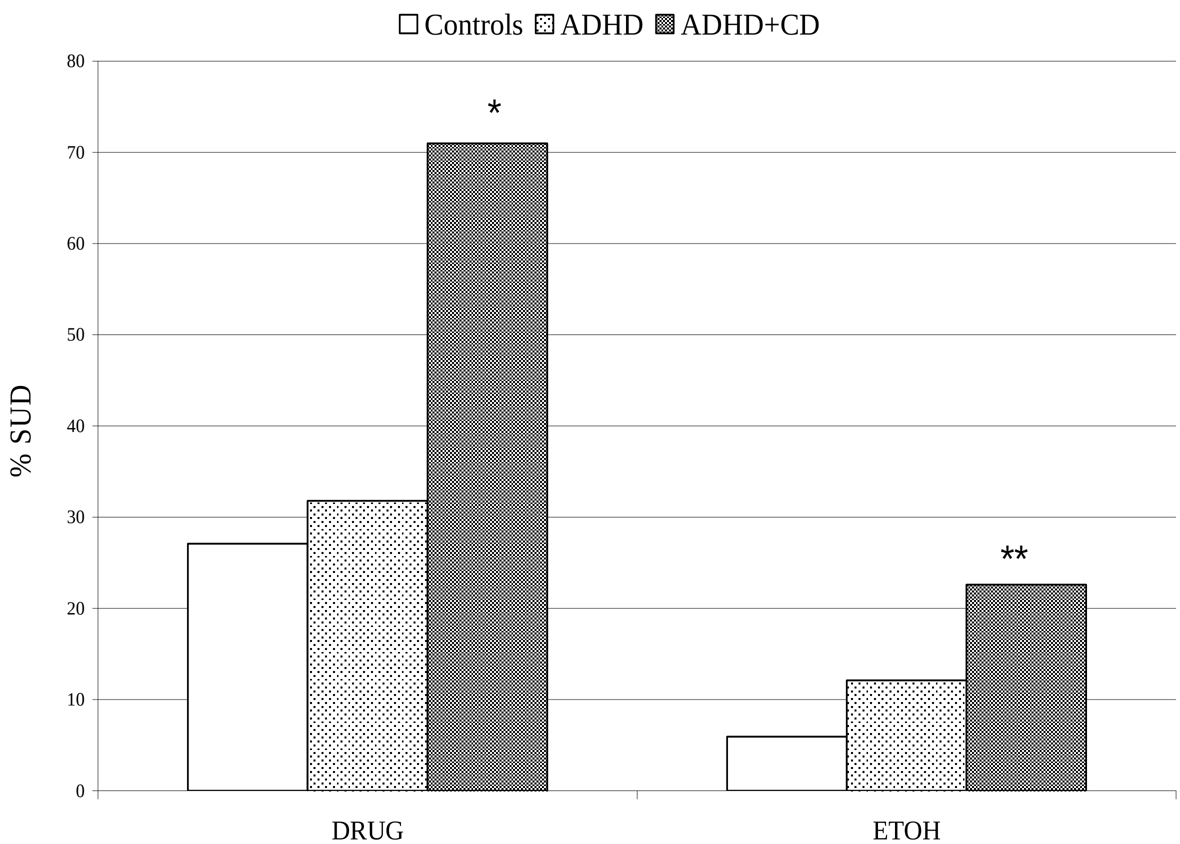
* = ADHD+CD group had significantly higher rates of 3-year cigarette and marijuana use severity when compared to the Control and ADHD-CD groups (all $p < .01$).

Logistic regression analyses of SUD outcomes are presented in Figure 5. A diagnosis of CD in childhood resulted in a significantly greater likelihood to have a drug use disorder by late adolescence relative to Controls (OR = 6.59, $p < .001$, $CI_{.95}$ = 2.65-16.39) and individuals diagnosed with ADHD but not CD (OR = 5.24, $p = .001$, $CI_{.95}$ =

2.06-13.31). A childhood diagnosis of CD resulted in a greater likelihood to have a late adolescent alcohol use disorder relative to Controls (OR = 4.67, p = .01, $CI_{.95}$ = 1.36-16.05), but not when compared to the ADHD group. The ADHD and Control groups did not differ on either measure of SUD.

Figure 5

Childhood Conduct Disorder predicts drug and alcohol SUD



* = ADHD+CD group had significantly higher rates of drug SUD when compared to the Control and ADHD-CD groups (all p < .01); ** = ADHD+CD group had significantly higher rates of alcohol SUD when compared to the Control group

Secondary analyses were conducted to assess the contribution of key group differences at baseline and follow-up. As such, among individuals diagnosed with ADHD with and without CD, further analyses were generated controlling for childhood differences in teacher rated ADHD symptoms (IOWA Conners I/O), childhood internalizing disorders (Mood/Anxiety), and SES. Secondary analyses were also conducted examining adolescent substance use severity and SUD as a function of group status while controlling for adolescent SES and FSIQ. Of the childhood variables controlled for, only childhood SES was found to be a significant predictor of adolescent cigarette ($p = .03$) and marijuana use ($p = .02$). SES in adolescence was associated with adolescent marijuana use ($p = .001$) and SUD ($p = .002$). However, primary outcomes were maintained across all secondary analyses.

As indicated in Table 6, duration of stimulant medication treatment, as assessed by the overall Wilks' Lambda, did not result in significant differences among the dimensional measures of substance use severity ($\lambda = .92$, $p = .79$), and there were no group differences in categorical drug ($X^2 = 1.84$, $p = .62$) or alcohol use disorders ($X^2 = 2.55$, $p = .47$).

Table 6

Percentage of SUD Diagnoses and 3-year Substance Use Severity as a function of Medication Subgroups

	None		One Year or Less		1-5 Years		Greater than 5 Years				
	n = 28		n = 19		n = 28		n = 22				
% Diagnosis									X^2	*p*	
ETOH	14.29		5.26		17.86		22.72		2.55	.47	
DRUG	35.71		52.63		50.00		40.91		1.84	.62	
Severity Index	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	*p*	η_p^2
Cigarettes	11.29	(17.70)	11.59	(13.06)	15.81	(14.75)	14.57	(16.01)	.51	.68	.02
Alcohol	24.86	(28.05)	23.37	(24.27)	31.85	(31.90)	30.38	(45.92)	.36	.78	.01
Marijuana	15.36	(20.91)	22.11	(26.68)	27.11	(28.90)	13.14	(18.11)	1.73	.17	.05
Other	3.68	(13.95)	3.05	(12.13)	4.26	(12.78)	4.62	(16.54)	.05	.99	.002

Discussion

The primary aims of this study were to further clarify the relationships among childhood CD, history of stimulant medication treatment, and late adolescent substance use behaviors in a sample of ethnically diverse urban adolescents from largely lower socioeconomic backgrounds. Consistent with findings generated from previous longitudinal studies (Barkley, Fischer, Edelbrock, & Smallish, 1990c; Molina & Pelham, Jr., 2003c; Molina, Bukstein, & Lynch, 2002c), our data indicate that childhood CD is a robust predictor of later substance abusing behaviors. Prior studies have suggested that ADHD symptomatology, in addition to CD, further increases risk for later substance using outcomes (Burke et al., 2001; Elkins et al., 2007; Milberger et al., 1997) while others suggest that CD mediates the relationship between ADHD and later substance misuse (Brook et al. 2010). Our data indicate that risk for later substance abuse is primarily carried by the childhood CD diagnosis and not ADHD per se. Those with childhood ADHD but not CD did not differ from the never-ADHD comparison group on any measure of later substance use.

Our two groups with childhood ADHD (i.e., with and with CD) did not differ on measures of parent-rated attention problems. While individuals diagnosed with CD in childhood had higher rates of teacher-rated ADHD symptoms, controlling for this variable did not alter the impact of CD on either dimensional or categorical measures of late adolescent substance misuse. Additionally, results revealed that the ADHD only group and Control group were similar on all measures of substance use severity and SUD status, further suggesting that in this sample of urban, largely minority youth, ADHD symptomatology alone did not portend late adolescent substance use outcomes.

Consistent with findings derived from most studies of middle class Caucasian samples (Barkley et al., 1990; Biederman et al., 2008), our data indicate that psychostimulant treatment neither increases risk nor serves as a protective factor in relation to later substance use. The variability in stimulant medication history in our sample allowed for the identification of four independent medication history groups of approximately equal size. Dividing the sample in this manner facilitates comparisons that improve upon the group distinctions seen in previous studies, and better approximates the variability in medication history seen clinically. The lack of impact on later substance use and abuse remained consistently non-significant whether categorical diagnostic or dimensional severity outcome measures were employed. Thus, it seems unlikely that the singular finding of Lambert and Hartsough (1998), indicating increased risk related to treatment, is due to the unique demographic characteristics of their sample.

This study has several key findings that further inform the literature on the impact of stimulant medication on later substance use, and provide insights into the misuse of substances among individuals with ADHD. That stimulant medication treatment was not found to impact later substance use replicates previous findings in the literature and extends these findings to an ethnically diverse urban sample of individuals with well characterized childhood comorbidity. Additionally, there was not a protective effect of treatment. This was the case even in the subgroup who received treatment for more than 5 years (on average nearly 9 years), in whom one would be most likely to see such an effect if it were present. Perhaps stimulant medication is only protective in adolescents who are actively being treated, as was largely the case in one previous study (Biederman et al. 1999).

The results of this study must be viewed within the context of several study limitations. First, and most importantly, we were unable to follow a substantial portion of the 169 youth who originally participated in the childhood study, although available data suggest that the sub-sample that was reevaluated was representative of the original group. Of note, this type of highly mobile urban sample of relatively low SES is very difficult to find once lost. In several cases, we were able to locate the parents, but often even they were unsure of their child's location. While we did manage to locate some of the cohort through social networking sites such as Facebook and My Space, in general, our greatest success on the internet was for locating those who were in prison and unavailable for reassessment. A second limitation is that the proportion of females in this study did not permit analysis of the possible gender differences in outcome measures. However, among those diagnosed with ADHD, there was no difference in the proportion of females with and without CD. Additionally, posthoc analyses conducted without female participants yielded results similar to the found in the full group. Third, we do not have childhood data for the Controls, since they were not recruited until the adolescent follow-up commenced and our determination that they never had ADHD is based solely upon retrospective assessment. Another possible limitation to this study is that SES may be confounded with childhood status; those with CD in childhood tended to have lower SES when compared to individuals with ADHD alone. It may be the case that the differences seen between groups on measures of adolescent substance use is not being driven by CD so much, but rather a function of higher SES serving as a protective factor. Lastly, the design of this study did not allow for evaluation/monitoring of adherence to treatment. This is potentially problematic given our findings that stimulant treatment had no effect on later substance misuse – since the negative finding could be in part attributable to poor adherence to treatment. Treatment adherence has been shown to be problematic in individuals with ADHD being treated with stimulants (Pappadopulos et al., 2009), and this is a concern for any study that attempts to elucidate the impact of stimulant treatment on later outcome.

Conclusion

The results of this study extend the findings that stimulant medication treatment does not significantly impact later substance using behaviors by examining this question in a sample of ethnically diverse urban adolescents/young adults and in a subgroup that received treatment for an extended period of time. In addition, results examining differences in SUD and substance use severity suggest that among individuals diagnosed with ADHD, a comorbid diagnosis of CD increases the risk for experiencing drug-related poor outcomes and impairment; those with ADHD without comorbid CD may not be at elevated risk for later substance misuse relative to their never ADHD peers.

Study III: Delinquency, aggression and attention-related problem behaviors differentially predict adolescent substance use in individuals diagnosed with ADHD.

A childhood diagnosis of attention-deficit/hyperactivity disorder (ADHD) has been repeatedly associated with elevated rates of adolescent and young adult substance use and substance use disorders (SUDs) (Mannuzza et al., 1998; Schubiner et al., 2000; Elkins et al., 2007; Milberger et al., 1997). Among individuals diagnosed with ADHD in childhood, the likelihood of late adolescent/young adult maladaptive substance use has been shown to be positively associated with the presence of comorbid conduct disorder (CD) (Barkley et al., 1990; Molina & Pelham, Jr., 2003; Molina et al., 2002). Previous studies have shown that between 30-50% of individuals diagnosed with ADHD also meet criteria for co-occuring CD (Biederman et al., 1991). Some studies have shown an association between ADHD and increased substance use over and above the risk posed by CD (Burke et al., 2001; Elkins et al., 2007; Milberger et al., 1997), while others have proposed that CD mediates the relationship between ADHD and later substance misuse (Brook, Brook, Zhang, & Koppel, 2010). As such, the degree to which ADHD and CD are independently associated with later substance use remains unclear. Past research has shown that behaviors associated with ADHD and CD are inter-correlated, but maintain a degree of independence in terms of etiology and developmental course (Waschbusch, 2002). It may be that ADHD and CD together generate a greater risk for later substance misuse than either disorder alone (Flory et al., 2003). What is clear from these studies, however, is that there is overwhelming evidence that suggests that a key role of CD in the emergence of substance use outcome in individuals diagnosed with ADHD.

Externalizing behaviors, which make-up the diagnosis of CD, can be divided into the two distinct dimensions: 1) aggressive behavior directed towards people and animals, and 2) delinquent acts such as coercive lying and vandalism (American Psychiatric Association, 2000). In combination these externalizing behaviors have been shown to predict a number of adverse outcomes, including adolescent and adult substance use (Fergusson, Horwood, & Ridder, 2005; Hawkins, Catalano, & Miller, 1992; Lynskey & Fergusson, 1995; Timmermans, van Lier, & Koot, 2008). Similarly, adolescents and young adults with substance use disorders exhibit high rates of externalizing behaviors (Diaz et al., 2011) and related psychiatric diagnoses, such as Antisocial Personality Disorder (Compton, Thomas, Stinson, & Grant, 2007).

Several studies have examined the relationship between the components of childhood externalizing behaviors (i.e., aggression and delinquency) and late adolescent/young adult substance use outcomes in non-clinical populations. Many have concluded that delinquent behavior throughout childhood development is the stronger predictor of later maladaptive substance use (Hayatbakhsh et al., 2008; Lynne-Landsman, Graber, Nichols, & Botvin, 2011; Mayzer et al., 2009). However, others have found that the stability of physical aggression (Timmermans et al., 2008) best predicts later use.

While past longitudinal studies examining the long-term outcomes of a childhood diagnosis of ADHD have shown that co-occurring CD is associated with higher rates of later substance use, only one study, to our knowledge, has examined the degree to which delinquent behaviors are specifically associated with later substance use in this population. Molina et al. (2007) employed both dimensional measures of delinquency and categorical CD diagnosis at baseline to examine delinquent and substance use behaviors in children enrolled the Multimodal Treatment Study of Children with ADHD (MTA) 24 and 36 months post treatment. Results showed that individuals diagnosed with ADHD displayed higher rates of delinquency and substance use in early adolescence when compared to the control group. Further, this study, which did not specifically look at aggression, reported that delinquency predicted substance use involvement at both 24- and 36-month time-points and CD predicted substance use at the 24 month time point only.

To our knowledge, this is the first study to specifically examine differential associations of aggression and delinquency in youth with ADHD to maladaptive substance use. As individuals with ADHD exhibit higher rates of externalizing behaviors in childhood and substance use behaviors in adolescence when compared to those without ADHD, gaining a better understanding of the predictive nature of such childhood behaviors can serve to inform preventive interventions targeting substance use behaviors.

The objective of this prospective 10-year follow-up study of ethnically and racially diverse urban youth from lower socioeconomic backgrounds diagnosed with ADHD in childhood was to measure the degree to which dimensional measures of attention, aggression and delinquency, as rated by parents in childhood and adolescence, and adolescent self-reports at follow-up, were differentially associated with late adolescent substance use outcomes.

Methods and Materials

Participants

Ninety-seven adolescents/young adults who were evaluated in a research protocol during childhood (mean age at baseline = 9.05 years, *SD* = 1.28), were seen for follow-up on average 9.30 (*SD* = 1.65) years later. They were drawn from a group of 169 youth who were recruited between 1990 and 1997 for a study of ADHD and aggression. Of these 169 participants, 18 refused to participate in the follow-up, two were known to be deceased, seven were incarcerated, and 45 were lost to follow-up. We attempted to locate missing participants by contacting known family members and via information publicly available on the internet. However, this sample was drawn from a highly mobile inner-city population and many individuals could not be found. Nevertheless, those who were and were not assessed at follow-up did not differ significantly with regard to age at initial evaluation, rates of childhood comorbid diagnoses, Full Scale IQ, socio-economic status (SES), or ADHD and other disruptive behavior disorder ratings at initial assessment (all $p > .10$). Thus, although a substantial number of the original sample was lost to follow-up, the sub-sample that participated in the follow-up study appears to be representative of the larger group.

Childhood Assessment

At baseline (ages 7 – 11 years), participants were evaluated using parent report on the Diagnostic Interview Schedule for Children (DISC) and the Child Behavior Checklist (CBCL). The CBCL is a frequently used parent report measure that assesses the dimensional nature of child emotional and behavioral difficulties (Achenbach, 1991). Individual items are collapsed into syndrome subscales such as Attention Problems, some of which are then further collapsed into the larger Internalizing (Withdrawn; Somatic Complaints; Anxious/Depressed) and Externalizing (Delinquency; Aggression) scales. Past research has shown that the CBCL is correlated with disorders seen in childhood such that there are clear associations between CBCL attention score and a diagnosis of ADHD and the delinquent behavior scale and a diagnosis of CD (Biederman et al., 1993; Biederman, Monuteaux, Kendrick, Klein, & Faraone, 2005). To insure cross-situationality of ADHD symptoms, children were required to have teacher ratings on the inattention/overactivity scale of the IOWA Conners (Pelham, Milich, Murphy, & Murphy, 1989) greater than 1.5 SD above the mean for age and gender.

This childhood sample was predominately male (88.8%) and racially and ethnically diverse (27.6% African-American, 24.5% Caucasian, 30.6% Hispanic, and 10.2% mixed or other ancestry). Mean socioeconomic status, estimated from parental occupation and education using the socioeconomic prestige scale (Nako K et al., 1994), was 36.92 (*SD* = 17.42), representing a low-middle status group. As shown in Table 7, the ADHD sample was overall, of average intellectual ability in childhood. As expected of a clinically-referred sample of youth with ADHD, they displayed elevated parent ratings (T $\geq$ 65) of attention problems and externalizing (delinquency and aggression) behaviors, and had high rates of other comorbid psychiatric disorders.

Follow-up Assessment

Ages of this late adolescent sample generally ranged from 16 to 22 years, however two individuals had follow-up ages of 25 and 26, and one was 15. As part of this follow-up evaluation, accompanying parent (n = 88, 91%) and participants (n = 85, 88%) successfully completed the CBCL and Youth Self-Report (YSR) which is the self-report version of the CBCL (Achenbach, 1991). Demographic and clinical characteristics of the sample at follow-up are shown in Table 8.

Table 7

Childhood Characteristics

	ADHD	
	(*n* = 97)	
Measure	Mean	SD
Age	9.05	1.28
SES	36.34	17.89
WISC IQ Full Scale	93.96	14.27
CBCL		
Attention problems	72.43	10.01
Externalizing	70.03	11.27
Delinquency	68.42	9.71
Aggression	72.63	14.01
IOWA Conners		
I/O	11.30	3.19
O/D	8.18	4.69
DISC		
%CD	32.7	
% ODD	47.9	
% ANX	31.6	
% MOOD	10.2	

Note: SES = Socioeconomic Status; WISC-R/III = Wechsler Intelligence Scale for Children, Revised/3rd Ed ;CBCL = Child Behavior Checklist; I/O = Inattention/Overactivity; O/D =Oppositional/Defiant; DISC = Diagnostic Interview Schedule for Children; CD = Conduct Disorder, ANX = any anxiety disorder; MOOD = any mood disorder.

Table 8
Late Adolescent Characteristics

	ADHD	
	(*n* = 97)	
Measure	Mean	SD
Age	18.43	1.78
SES	43.25	17.97
WAIS IQ -Full Scale	93.29	14.94
CBCL		
Attention problems	61.44	10.39
Externalizing	60.73	12.99
Delinquency	61.83	10.48
Aggression	62.57	11.95
YSR		
Attention problems	57.46	9.59
Externalizing	58.62	11.64
Delinquency	61.40	8.96
Aggression	59.07	10.29

Note: SES = Socioeconomic Status; WAIS = Wechsler Adult Intelligence Scale 3rd Ed; CBCL = Child Behavior Checklist; YSR = Youth Self Report

Participants and their parents were proficient in English, and were compensated for their time and travel. All procedures were approved by the Institutional Review Boards of the participating institutions. Written informed consent was obtained from all adolescents above the age of 18 years and the parents of those under the age of 18 years. Assent was obtained from youth under 18 years-old.

Substance Use Status

Determination of substance use disorder (SUD) and alcohol use disorder (AUD) status was made using the Kiddie-SADS –PL (Kaufman et al., 1997), which was administered at follow-up to each adolescent, and separately to each participant’s parent. Forty three percent of individuals in this sample met criteria for a SUD and 15% met criteria for an AUD. Following DSM-IV guidelines, SUDs were defined as disorders resulting from illicit drug misuse and AUDs were defined as disorders resulting from maladaptive alcohol use. Evaluators were Ph.D. level psychologists or trained psychology graduate students blind to childhood status. Responses were combined across interviewee by item; if either informant indicated that the item caused significant distress or impairment, the symptom was judged to be present. Diagnoses of drug and alcohol abuse and dependence, past and present, were collapsed into binary (yes/no) categories that combined diagnoses of abuse and dependence.

Severity of substance use was assessed using the Rutger's Alcohol and` Drug Use Questionnaire (Labouvie et al., 1997). Adolescents (n = 95, 98%) were asked to report use of cigarettes, alcohol, and marijuana over the past 3 years. The Rutger's substance use screening measure asks adolescents about the frequency (how often) and intensity (amount) of substance use. For example, at the beginning of the cigarette use module participants were asked if they had smoked a whole cigarette at least one time during the preceding 3 years. If they indicated that they had smoked during that time they were asked to indicate the frequency (1-2 times, 3-9 times….1000 or more times) and intensity of their use when they smoked (less than 1 a day, 1-4 cigarettes,…More than 2 packs). Similar to Labouvie et al. (1997), severity of substance use was defined as the product of frequency x intensity of use. As such, indicators of substance use frequency and intensity were itemized and a product was obtained, resulting in a unitary dimensional measure of substance use severity for each drug class. All severity variables were square root transformed to normalize their distributions

Statistical Analysis:

Pearson product-moment correlation coefficients were generated to assess the degree of association among the predictor variables. Hierarchical binary logistic and hierarchical linear regressions were employed to measure the degree to which the externalizing behaviors of delinquency and aggression, and problems with attention, were differentially associated with late adolescent SUD/AUD status and substance use severity, respectively. In all analyses, SES and age at follow-up were entered as control variables in the first block and CBCL/YSR ratings (delinquency, aggression, attention problems) were entered as either childhood predictor variables (parent ratings in childhood) or adolescent correlates (parent/youth ratings in adolescence) in the second block. All variables were entered using Forced Entry. The results of categorical substance use outcomes are presented as odds ratios (ORs) together with 95% confidence intervals (CIs) as the indicator of statistical significance.

Results

As seen in Table 9, parent and adolescent report of delinquency, aggression, and attention problems were significantly correlated. However, measures of colinearity, calculated on all linear regressions, resulted in an acceptable range of Variance Inflation Factor (VIF) with scores between 1.01 and 3.16. As indicated in Tables 10-13, age at follow-up and childhood SES were both significantly associated with adolescent substance use outcomes.

Table 9

Correlations among Predictor Variables

	C-DEL	C-AGG	C-ATTN	A-DEL	A-AGG	A-ATTN	Y-DEL	Y-AGG	Y-ATTN
C-DEL	1.00	.76**	.51**	.36**	.14	.19	.20	.01	.02
C-AGG		1.00	.63**	.18	.19	.24**	.16	.13	.12
C-ATTN			1.00	.05	.15	.30**	.03	.12	.25*
A-DEL				1.00	.75**	.66**	.53**	38**	.21
A-AGG					1.00	.75**	.38**	.47**	.19
A-ATTN					.	1.00	.31**	.39**	.30**
Y-DEL							1.00	.65**	.52**
Y-AGG								1.00	.74**
Y-ATTN									1.00

Note: C- = CBCL in Childhood; A- = CBCL in Adolescence; Y- = YSR in Adolescence;
DEL = Delinquency; AGG = Aggression; ATTN = Problems with Attention
* = p ≤ .05
** = p ≤ .01

Childhood Predictors

As can be seen in Table 10, childhood delinquency and aggression, but not attention, were positively correlated with adolescent substance use. As shown in Tables 11 and 12, after controlling for childhood SES and age at adolescent follow-up, parent ratings of delinquency in childhood were a significant predictor of adolescent substance use outcome. Delinquency severity significantly predicted adolescent SUD status and 3-year cigarette and marijuana use severity. Neither childhood aggression nor attention problems, after accounting for the other variables in the model, predicted late adolescent substance use diagnostic status.

Table 10

Correlation between Childhood Predictor Variables and Adolescent Substance Use Outcomes

	C-DEL	C-AGG	C-ATTN
Cigarette Use	.41**	.32**	.13
Alcohol Use	.10	.05	-.02
Marijuana Use	.37**	.23*	-.05
SUD	.26*	.11	-.06
AUD	.11	.02	-.07

Note: C- = CBCL in Childhood; DEL = Delinquency; AGG = Aggression; ATTN = Problems with Attention
* = $p \leq .05$
** = $p \leq .01$

Table 11

Predictors and correlates of adolescent diagnostic status

A. Predictors and correlates of adolescent SUD outcome, OR (95% CI)

	Childhood CBCL	Adolescent CBCL	Adolescent YSR
SES	.97 (.94 -1.00)*	.96 (.93 -1.00)*	.97 (.93 -1.01)
Adolescent age	1.21 (.91-1.61)	1.40 (.93 - 2.01)	1.58 (.94 - 2.63)
Delinquency	1.10 (1.02-1.19)*	1.20 (1.09-1.33)*	1.27 (1.13-1.43)*
Aggression	.99(.93-1.04)	.96(.89 – 1.04)	.94 (.86 – 1.04)
Attention Problems	.95 (.89 -1.04)	.93 (.85 - 1.02)	.99 (.91 - 1.09)

Note: SUD = Substance Use Disorder; OR = Odds Ratio, CI = Confidence Interval
* = $p \leq .05$

B. Predictors and correlates of adolescent AUD outcome, OR (95% CI)

	Childhood CBCL	Adolescent CBCL	Adolescent YSR
SES	1.01 (.98 -1.05)	1.01 (.96 -1.07)	.99 (.95 -1.04)
Adolescent age	1.41 (1.02-1.94)*	1.41 (.79 -2.48)	1.42 (.82 - 2.44)
Delinquency	1.07 (.96-1.20)	1.24 (1.06-1.45)*	1.08 (.97-1.21)
Aggression	.99(.92-1.07)	1.01(.93 – 1.10)	1.00 (.90 – 1.11)
Attention Problems	.95 (.87 -1.03)	.78 (.64 - .94)*	.94 (.83 - 1.06)

Note: AUD = Alcohol Use Disorder; OR = Odds Ratio, CI = Confidence Interval
* = $p \leq .05$

Table 12

Childhood predictors of adolescent substance use severity

Cigarette Use	B	β	t	p	r^2
SES	-.02	-.11	-1.22	.23	
Age at follow-up*	.51	.35	3.90	<.01	.19⁺
Delinquency*	.09	.33	2.40	.02	
Aggression	.02	.11	.74	.46	
Attention Problems	-.04	-.16	-1.35	.18	.31⁺⁺
Alcohol Use	B	β	t	p	r^2
SES	.02	.14	1.37	.17	
Age at follow-up*	.61	.33	3.28	<.01	.13⁺
Delinquency	.04	.12	.75	.46	
Aggression	.04	.07	.45	.66	
Attention Problems	-.06	-.18	-1.44	.15	.16⁺⁺
Marijuana Use	B	β	t	p	r^2
SES	-.03	-.19	-1.94	.06	
Age at follow-up	.24	.14	1.44	.15	.10⁺
Delinquency*	.13	.41	2.84	<.01	
Aggression	.01	.06	.38	.71	
Attention Problems*	-.09	-.30	-2.45	.02	.24⁺⁺

Note: * = $p \leq .05$; $^{+}$ = variance that can be attributed to SES and Age at follow-up; $^{++}$ = total variance accounted for by control and predictor variables.

After accounting for delinquency and aggression ratings, childhood attention problems were negatively associated with severity of late adolescent marijuana severity, but not cigarette use severity or SUD status. Delinquency, aggression, and attention problems as assessed in childhood did not predict adolescent alcohol use severity or diagnostic status.

Adolescent Concurrent Correlates

As can be seen in Table 13, Pearson product moment and Point-biserial correlations revealed that parent report of delinquency, but not aggression or attention problems, was associated with cigarette and marijuana use severity and SUD status. Similarly, parent report of delinquency in adolescence, after controlling for childhood SES and age at follow-up, was significantly associated with all measures of adolescent substance use. Parent rating of adolescent aggression was negatively associated with adolescent marijuana use severity and was not associated with any other outcome measure. Report of adolescent attention problems was negatively associated with the categorical AUD status, and dimensional ratings of 3-year cigarette, alcohol, and marijuana use severity. [see Tables 11 and 14].

Table 13

Correlation between Adolescent Delinquency, Aggression, Attention Problems and Substance Use as Rated by Parent

	A-DEL	A-AGG	A-ATTN
Cigarette Use	.40**	.21	.06
Alcohol Use	.15	.01	-.15
Marijuana Use	.48**	.15	.02
SUD	.41**	.18	_-.13
AUD	.14	.02	.08

Note: A- = CBCL in Adolescence; DEL = Delinquency; AGG = Aggression; ATTN = Problems with Attention
* = $p \leq .05$
** = $p \leq .01$

Table 14

Adolescent correlates (Parent) of adolescent substance use severity:

Cigarette Use	b	β	t	p	r^2
SES	-.02	-.16	-1.85	.07	
Age at follow-up*	.78	.42	4.74	<.01	.20⁺
Delinquency*	.17	.66	4.88	<.01	
Aggression	-.02	-.08	-.52	.62	
Attention Problems*	-.08	-.31	-2.3	.02	.42⁺⁺
Alcohol Use	b	β	t	p	r^2
SES	.01	.06	.57	.57	
Age at follow-up*	.85	.36	3.69	<.01	.14⁺
Delinquency*	.14	.47	3.09	.003	
Aggression	-.01	-.04	-.24	.81	
Attention Problems*	-.13	-.41	-2.73	.01	.27⁺⁺
Marijuana Use	b	β	t	p	r^2
SES*	-.05	-.25	-3.26	<.01	
Age at follow-up*	.73	.33	4.25	<.01	.19⁺
Delinquency*	.26	.92	7.73	<.01	
Aggression*	-.07	-.29	-2.14	.04	
Attention Problems*	-.11	-.37	-3.15	<.01	.55⁺⁺

Note: * = $p \leq .05$; $^{+}$ = variance that can be attributed to SES and Age at follow-up; $^{++}$ = total variance accounted for by control and predictor variables.

Pearson product moment and Point-biserial correlations revealed that adolescent report of delinquency, but not aggression or attention problems was associated with cigarette and marijuana use severity and SUD status (see table 15). Youth report of adolescent delinquency was significantly associated with late adolescent SUD status as well as measures of cigarette, alcohol, and marijuana use severity. Adolescent attention problems, as rated by youth, while not associated with measures of diagnostic status, were negatively associated with report of 3-year alcohol and marijuana use severity. (see Tables 11 and 16).

Table 15

Correlation between Adolescent Delinquency, Aggression, Attention Problems and Substance Use as Rated by Adolescent

	Y-DEL	Y-AGG	Y-ATTN
Cigarette Use	.44**	.09	.04
Alcohol Use	.17	-.14	-.21
Marijuana Use	.47**	.08	-.03
SUD	.58**	.19	.15
AUD	.19	.01	-.03

Note: Y- = YSR in Adolescence; DEL = Delinquency; AGG = Aggression; ATTN = Problems with Attention
* = $p \leq .05$
** = $p \leq .01$

Table 16

Adolescent correlates (Youth) of adolescent substance use severity:

Cigarette Use	b	β	t	p	r^2
SES	-.02	-.12	-1.07	.29	
Age at Follow-up*	.65	.34	3.36	<.01	.23$^+$
Delinquency*	.12	.48	3.58	<.01	
Aggression	-.03	-.13	-.78	.43	
Attention Problems	-.03	-.10	-.71	.48	.35^{++}
Alcohol Use	b	β	t	p	r^2
SES	.01	.07	.70	.48	
Age at Follow-up*	.79	.33	3.14	<.01	.19$^+$
Delinquency*	.13	.36	2.51	.01	
Aggression	-.04	-.13	-.79	.43	
Attention Problems	-..09	-.26	-1.79	<.01	.28^{++}
Marijuana Use	b	β	t	p	r^2
SES*	-.04	-.22	-2.30	.02	
Age at Follow-up*	.58	.25	2.63	.01	.25$^+$
Delinquency*	.19	.56	4.33	<.01	
Aggression	-.03	-.09	-.56	.57	
Attention Problems*	-.08	-.26	-1.98	.05	.42^{++}

Note: * = $p \leq .05$; $^+$ = variance that can be attributed to SES and Age at follow-up; $^{++}$ = total variance accounted for by control and predictor variables.

Discussion

This study sought to address the degree to which dimensional parent ratings of delinquency and aggression, along with problems of attention, measured in childhood uniquely predict later diagnostic and dimensional substance use outcomes in adolescence. It also examined the degree to which parent and youth ratings of delinquency, aggression, and attention problems were associated with concurrent maladaptive substance use in adolescence. Pearson product-moment correlations revealed that, regardless of rater and time-point, delinquency, aggression, and attention problems were highly inter-correlated.

Such results were not surprising as all three measures are notable for dysregulated behaviors and past studies have demonstrated that conduct and attention related difficulties are inter-related (Waschbusch, 2002). Also notable in these correlations were strong rater and temporal effects. Ratings of different dimensions by the same rater (i.e., parent or child), and ratings derived at the same time point (i.e, adolescence), were more highly inter-correlated. However, while these behaviors were correlated, VIF scores were found to be in the normal range, indicating that collinearity was not an issue preventing the analyses in this study.

Overall, results generated two notable findings: 1) Delinquency, but not aggression, is a robust predictor and concurrent correlate of adolescent substance use outcomes in individuals diagnosed with ADHD in childhood, and 2) After controlling for delinquency and aggression, attention problems were negatively associated with multiple measures of substance use outcomes.

That delinquency was such a robust predictor and correlate of outcome supports previous findings seen in prospective longitudinal studies (Molina et al., 2007; Hayatbakhsh et al., 2008). Effect sizes generated for dimensional and categorical outcomes (r^2/OR) were generally in the moderate range, supporting the idea that delinquency is a robust and stable predictor and correlate of adolescent substance using behaviors.

Interestingly, while a robust predictor of other substance (i.e., drug) use outcomes, childhood delinquency did not predict AUD status or alcohol use severity. Prior studies have shown delinquent behavior in childhood to be predictive of later alcohol related outcomes (Chartier, Hesselbrock, & Hesselbrock, 2010; Clark et al., 2005; Clark et al., 2008). However, studies examining such outcomes in individuals diagnosed with ADHD have generated equivocal findings, with several studies finding no difference in adolescent alcohol use behaviors when compared to controls (Biederman et al., 1997; Molina & Pelham, Jr., 2003). It has been suggested that individuals diagnosed with ADHD may demonstrate a different developmental profile as related to alcohol use outcomes (Molina, Pelham, Gnagy, Thompson, & Marshal, 2007). The current sample, similar to those in the Biederman et al (1997) and Molina and Pelham (Molina et al., 2003) studies cited above, had a mean age of 18.42 (SD = 1.78), with approximately 95% of the sample under the legal drinking age. As such, it may be that late adolescence is too early in the developmental course in which to predict alcohol related outcomes.

Our findings suggest that unlike delinquency, aggression, as measured by the CBCL and YSR, is neither a predictor nor a correlate of late adolescent substance use. Of the 15 analyses conducted in this study that included aggression as an independent variable, only one generated a significant result and the finding was in the opposite direction. It is hard to know what to make of the finding that adolescent aggression, as rated by parents, is negatively correlated with adolescent marijuana use severity when all other analyses that employed aggression as an independent variable failed to generate significant effects. As the effect size was relatively small ($\beta = -.29$; $p = .04$), it is likely that this finding might represent a Type I error.

Previous studies examining the predictors of later substance use outcomes in individuals with ADHD have generated conflicting findings regarding the role of attention related difficulties. Of the studies that have reported a positive relationship between problems with attention and substance use, some have shown that inattentive behaviors best predict later substance use outcomes (Burke et al., 2001; Molina et al., 2003a), while others have shown that hyperactivity/impulsivity better accounts for substance use outcomes (Elkins et al., 2007; Lee & Hinshaw, 2006). The current study did not examine the behaviorial symptoms that comprise a diagnosis of ADHD and the attention problems syndrome scale on both the CBCL and YSR contains inattentive ("can't concentrate, can't pay attention for long") and hyperactive/impulsive ("can't sit still, restless, or hyperactive") behaviors. However, that a validated measure of attention problems (Achenbach, 1991), shown to be correlated with diagnostic status (Biederman et al., 1993), fails to predict substance use outcomes furthers the argument that ADHD-related symptoms, independent of conduct problems are not primary predictors of outcome.

In fact, high levels of Attention Problems, as measured by both the CBCL and YSR, frequently emerged as a negative predictor of substance using behavior. Unlike the singular finding with Aggression, the frequency with which this negative association emerged makes it unlikely to be a Type I error. Thus, within this sample, it appears that after accounting for delinquent and aggressive behaviors, high levels of ADHD symptoms *reduce* the likelihood of drug- and alcohol-seeking behaviors. While an explanation for such findings remains speculative at this time, one possibility is that among children with ADHD who are raised in an inner-city, largely lower socio-economic environment, those who remain resistant to the environmental factors that increase rates of aggression and delinquency are particularly resilient and similarly resist an entry into substance use. If true, research identifying protective factors will be particularly important to the development of preventive interventions within such environments.

The results of this study must be viewed within the context of several limitations. First, and most importantly, we were unable to follow all 169 youth who originally participated in the childhood study, although available data suggest that the sub-sample that was reevaluated was representative of the original group. Second, of the 97 individuals that participated in the follow-up assessment, 88 (91%) parents and 85 participants (88%) completed the CBCL and YSR, respectively. These findings would benefit from a replication study on a larger sample of youth with ADHD and a matched control sample.

By examining three types of behaviors associated with maladaptive substance use, this study extended previous findings that delinquency is a robust predictor and correlate of adolescent/young adult substance use outcome. Behaviors of aggression, which along with delinquency constitute the diagnostic criteria of CD, itself a robust predictor of maladaptive drug use, was not associated with outcome. As such, future studies examining predictors of substance use such as CD may wish to examine the factors that contribute to the initiation and expression of delinquent behavior. Problems with attention were negatively associated with substance use outcomes, suggesting that among individuals diagnosed with ADHD, difficulties with the initiation and maintenance of attention does not increase the risk for experiencing drug-related poor outcomes and impairment.

GENERAL DISCUSSION

This series of studies was conducted to better understand impulsive and dysregulated behaviors and their association with maladaptive drug use. We explored this topic in both animal and human samples. The impact of chronic drug use on impulsive choice was examined in rats exposed to heroin, and human studies examined the impact of psychostimulant treatment on a range of late adolescent substance use outcomes. Human studies additionally examined the degree to which childhood diagnoses of ADHD and CD and ratings of aggression, attention, and delinquency, all of which are associated with impulsivity, in childhood and adolescence were related to adolescent substance use outcomes in youth diagnosed with ADHD. Human studies were conducted in an ethnically-diverse, lower SES sample of urban youth who were diagnosed with ADHD in childhood, and a group of well-matched community controls recruited in adolescence.

Overview of Study Findings

Study I was designed to measure alterations in impulsive choice through a delay discounting paradigm as a function of chronic heroin administration. Cross-sectional studies in humans have revealed that individuals meeting criteria for an SUD demonstrate a higher level of impulsive behavior in a choice paradigm where there are two possible rewards (immediate/small: large/delayed). As these studies are naturalistic by design, it is unclear if differences in choices are due to differences in baseline impulsivity or a result of prolonged and sustained substance use. Animal studies, which are well-suited to address the degree to which sustained drug use impact impulsive behavior, have generated mixed findings (Paine et al., 2003; Roesch et al., 2007; Simon et al., 2007) in relation to the degree to which chronic drug administration impacts impulsive behavior. Animals were trained on a delay discounting paradigm and were then treated with either heroin or saline for 12 days. Three days after the last injection animals were again placed in operant chambers and experienced the terminal delay discounting sequence. Heroin-treated animals exhibited significant progressive increases in locomotor activity indicating that they had become sensitized to the drug. Heroin- and saline –treated groups did not differ in performance across delay conditions either before or after chronic treatment periods. These results indicate that chronic heroin intake does not impact later impulsive responding for natural (food) reward.

Study II examined late adolescent substance use outcomes in urban youth diagnosed with ADHD in childhood as a function of childhood CD and psychostimulant treatment. This study attempted to further clarify roles of impulsive and dysregulated behaviors by clarifying areas that are currently unclear in the current literature. While CD has been shown to be a robust predictor of substance use outcome in individuals with ADHD, most of these studies have been conducted with primarily Caucasian youth (Biederman et al., 1991; Mannuzza et al., 1998). Similarly, studies examining the degree to which psychostimulant treatment impacts later drug use have generated equivocal findings (Barkley et al., 2003; Biederman et al., 1999; Lambert & Hartsough, 1998). We hypothesized that individuals diagnosed with ADHD and CD would exhibit more severe substance using behaviors when compared to individuals with ADHD without CD and to a well-matched control group. Further, among individuals diagnosed with ADHD in childhood, stimulant medication, regardless of duration of use and the presence/absence of comorbid CD, would not differentially impact later substance use severity and risk for SUD. As hypothesized, individuals with ADHD+CD in childhood had significantly higher rates of SUD and substance use severity as compared to those with childhood ADHD-CD and controls. Among those with childhood ADHD, there were no significant differences in SUD status or substance use severity as a function of medication history.

Study III focused on the degree to which ratings of aggression, attention problems, and delinquency in childhood and adolescence are related to adolescent substance use outcomes in youth diagnosed with ADHD. As shown in Study II, CD is a potent predictor of substance use outcomes. The behaviors that constitute the symptoms of CD can be divided into two distinct dimensions, aggression and delinquency. Studies examining the degree to which attention problems are associated with maladaptive substance use, especially in relation to CD, have generated equivocal findings (Barkley et al., 2003; Burke et al., 2001; Elkins et al., 2007; Milberger et al., 1997; Molina et al., 2003). We identified a robust relationship between childhood and adolescent delinquency and adolescent substance use. Aggression was not associated with adolescent substance use outcomes and problems with attention were found to be negatively associated with outcome. Results must be viewed within the context of the study. These behaviors are highly inter-correlated. As such, a conservative interpretation of findings would clearly indicate that, of the three, delinquency is the most potent predictor of adverse outcome. The frequently emerging negative association between attention problems and substance use warrants further investigation.

Together, these studies sought to examine the relationship of impulsive and dysregulated behaviors to substance use. Study I examined the degree to which impulsivity is predicted by drug use. In animals, chronic administration of heroin did not result in an increase in impulsive behavior. Study II also addressed the degree to which drug use (psychostimulants) resulted in alterations in behavior. Here, the dependent variable was not impulsive behavior per se, but substance use, which was not shown to be impacted by psychostimulant use. While not a main aim of the study, it is important to note that there were no significant differences in internalizing or externalizing behaviors as a function of medication use, suggesting that psychostimulant treatment did not result in systematic changes in behavior.

Studies II and III examined the degree to which trait impulsivity predicted later drug use. In Study II, a childhood diagnosis of CD, but not ADHD, was significantly associated with greater substance using behaviors. Study III revealed that among individuals with ADHD, behaviors associated with delinquency, but not aggression or attention problems, best predicted substance use outcomes. These results support the idea that adolescent substance use can be predicted by childhood traits and that the best predictors are those associated with disruptive behaviors, like CD, but specific to delinquency.

The studies here did not specifically address the idea that both drug use and impulsivity are predicted by a third factor. However, individuals at risk for developing later substance using difficulties exhibit difficulties in both internalizing and externalizing psychological processes (Tarter et al., 2003). As such, it may be that that difficulties in regulatory behaviors may exist that subsume both impulsive/dysregulated behaviors and substance use. Such ideas are well suited for future research.

Directions for Future Research

Further identifying the core liabilities to maladaptive substance use is of critical importance. Previous studies have identified commonalities between substance use, externalizing disorders such as CD, and internalizing difficulties associated with major depressive disorder (Clark et al., 1997). A similar study (Martin, Lynch, Pollock, & Clark, 2000), identified two personality factors, Behavioral Undercontrol and Negative Emotionality, proposed to comprise a developmentally early phenotype of liability for later SUD. Factor items were comprised of a variety of interview and questionnaire questions assessing behaviors and emotions. Future studies may wish to further refine these findings by examining the independence of these factors as well as their developmental expression.

Studies examining the development and expression of antisocial behavior have identified “adolescent limited” and “life-course persistent” trajectories of anti-social/delinquent behavior (Moffitt, 1993). Future studies may wish to characterize individuals who express high but developmentally limited levels of impulsive and dysregulated behaviors from individuals characterized by relatively high and stable levels the same behaviors. Examining the relationship between the different trajectories of behaviors associated with impulsivity and delinquency and their relation to different expressions of maladaptive substance using patterns would further inform our understanding of a variety of substance using outcomes including SUD, desistance, and relapse behaviors.

Limitations

The results of the preceding studies should be interpreted in the context of several limitations that have been outlined in the conclusions of each study. In Study I, we measured impulsivity in a delay discounting paradigm where impulsivity was operationalized as the calculated delay to large reward at which the animal shows equal likelihood of choosing the delayed large reward or the immediate small reward (IP). However, impulsivity is a heterogeneous construct (Evenden, 1999) and it is possible that animals might exhibit differences in another measure of impulsivity. In this study animals received intra-peritoneal injections of either heroin or saline. There is evidence to suggest that the mode of administration may differentially impact the degree to which drugs affect the neural systems involved in reward-related behavior (Setlow et al., 2009). It is possible that animals would have performed differently if allowed to self-administer drug or if tested with a different substance (e.g., cocaine).

In Studies II and III, we were unable to follow a substantial portion of the 169 youth who originally participated in the childhood study. It is important to note that available data indicate that the sub-sample that was reevaluated was representative of the original group. This type of highly mobile urban sample of relatively low SES is very difficult to find once lost. A second limitation to these studies is that the proportion of females in this study did not permit analysis of the possible gender differences in outcome measures. However, among those diagnosed with ADHD, there was no difference in the proportion of females with and without CD. Another possible limitation to this study is that SES may be confounded with childhood status; those with CD in childhood tended to have lower SES when compared to individuals with ADHD alone. It may be the case that the differences seen between groups on measures of adolescent substance use is not being driven by CD so much, but rather a function of higher SES serving as a protective factor.

A further limitation in Study II is that there is no childhood data for the Controls, since they were not recruited until the adolescent follow-up commenced and our determination that they never had ADHD is based solely upon retrospective assessment. Additionally, the design of this study did not allow for evaluation/monitoring of adherence to treatment. This is potentially problematic given our findings that stimulant treatment had no effect on later substance misuse – since the negative finding could be in part attributable to poor adherence to treatment. Treatment adherence has been shown to be problematic in individuals with ADHD being treated with stimulants (Pappadopulos et al., 2009), and this is a concern for any study that attempts to elucidate the impact of stimulant treatment on later outcome. Lastly, of the 97 individuals that participated in Study III , 88 (91%) parents and 85 participants (88%) completed the follow-up CBCL and YSR, respectively.

Implications for Future Policy and Practice

These results further refine our understanding of the relationship that exists between impulsive and dysregulated behaviors and maladaptive substance use. Determining the specific risks factors that impact later delinquent and substance use outcomes allows practitioners to identify those children most at-risk and target prevention and treatment strategies more effectively. The findings from this present study have important implications with regard to delinquent behaviors and substance use outcomes. We identified trait impulsivity, as manifest in delinquent behavior, as a significant predictor of adolescent substance use outcomes. There has been a wealth of research and practice devoted to limiting the influence early expressions of impulsivity and aggression have on later outcome (Connor et al., 2006). These results suggest that specifically identifying and targeting impulsive behaviors related to the expression of delinquency may be a focus of continued efforts in the areas of preventative and psychosocial treatments.

Reference List

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. Burlington, VT: University of Vermont Department of Psychiatry.

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR, 4th ed.* Washington, DC: American Psychiatric Association.

Andersen, S. L., Arvanitogiannis, A., Pliakas, A. M., LeBlanc, C., & Carlezon, W. A., Jr. (2002). Altered responsiveness to cocaine in rats exposed to methylphenidate during development. *Nat.Neurosci.*, *5*, 13-14.

Anglin, M. D., Booth, M. W., Ryan, T. M., & Hser, Y. I. (1988). Ethnic differences in narcotics addiction. II. Chicano and Anglo addiction career patterns. *Int J Addict.*, *23*, 1011-1027.

Anglin, M. D., Ryan, T. M., Booth, M. W., & Hser, Y. I. (1988). Ethnic differences in narcotics addiction. I. Characteristics of Chicano and Anglo methadone maintenance clients. *Int J Addict.*, *23*, 125-149.

Armstrong, T. D. & Costello, E. J. (2002). Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. *J Consult Clin Psychol*, *70*, 1224-1239.

Baker, F., Johnson, M. W., & Bickel, W. K. (2003a). Delay discounting in current and never-before cigarette smokers: similarities and differences across commodity, sign, and magnitude. *J Abnorm.Psychol, 112,* 382-392.

Barkley, R. A., Fischer, M., Edelbrock, C. S., & Smallish, L. (1990). The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry, 29*, 546-557.

Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K. (2003). Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. *Pediatrics, 111,* 97-109.

Belin, D., Mar, A. C., Dalley, J. W., Robbins, T. W., & Everitt, B. J. (2008a). High impulsivity predicts the switch to compulsive cocaine-taking. *Science*, *320,* 1352-1355.

Bell, M. A. & Deater-Deckard, K. (2007). Biological systems and the development of self-regulation: integrating behavior, genetics, and psychophysiology. *J Dev.Behav Pediatr, 28,* 409-420.

Bickel, W. K. & Marsch, L. A. (2001). Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction, 96,* 73-86.

Biederman, J. (2003). Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: findings from a longitudinal follow-up of youths with and without ADHD. *J Clin Psychiatry, 64 Suppl 11,* 3-8.

Biederman, J., Faraone, S. V., Doyle, A., Lehman, B. K., Kraus, I., Perrin, J. et al. (1993). Convergence of the Child-Behavior Checklist with Structured Interview-Based Psychiatric Diagnoses of Adhd Children with and Without Comorbidity. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 34,* 1241-1251.

Biederman, J., Monuteaux, M. C., Kendrick, E., Klein, K. L., & Faraone, S. V. (2005). The CBCL as a screen for psychiatric comorbidity in paediatric patients with ADHD. *Archives of Disease in Childhood, 90,* 1010-1015.

Biederman, J., Monuteaux, M. C., Spencer, T., Wilens, T. E., Macpherson, H. A., & Faraone, S. V. (2008). Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. *Am J Psychiatry, 165,* 597-603.

Biederman, J., Newcorn, J., & Sprich, S. (1991a). Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *Am.J.Psychiatry, 148,* 564-577.

Biederman, J., Wilens, T., Mick, E., Faraone, S. V., Weber, W., Curtis, S. et al. (1997). Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 36,* 21-29.

Biederman, J., Wilens, T., Mick, E., Spencer, T., & Faraone, S. V. (1999). Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. *Pediatrics, 104,* e20.

Bornovalova, M. A., Daughters, S. B., Hernandez, G. D., Richards, J. B., & Lejuez, C. W. (2005). Differences in impulsivity and risk-taking propensity between primary users of crack cocaine and primary users of heroin in a residential substance-use program 166. *Exp.Clin Psychopharmacol., 13,* 311-318.

Boyle, M. H., Offord, D. R., Racine, Y. A., Fleming, J. E., Szatmari, P., & Links, P. S. (1993). Predicting substance use in early adolescence based on parent and teacher assessments of childhood psychiatric disorder: results from the Ontario Child Health Study follow-up. *J Child Psychol Psychiatry, 34,* 535-544.

Brook, D. W., Brook, J. S., Zhang, C., & Koppel, J. (2010). Association between attention-deficit/hyperactivity disorder in adolescence and substance use disorders in adulthood. *Arch.Pediatr Adolesc Med., 164,* 930-934.

Brook, J. S., Whiteman, M., Finch, S. J., & Cohen, P. (1996). Young adult drug use and delinquency: Childhood antecedents and adolescent mediators. *Journal of the American Academy of Child and Adolescent Psychiatry, 35,* 1584-1592.

Buckner, J. D. & Schmidt, N. B. (2009). Social anxiety disorder and marijuana use problems: the mediating role of marijuana effect expectancies. *Depress.Anxiety.*.

Buckner, J. D. & Schmidt, N. B. (2009b). Understanding social anxiety as a risk for alcohol use disorders: fear of scrutiny, not social interaction fears, prospectively predicts alcohol use disorders. *J Psychiatr Res, 43,* 477-483.

Burke, J. D., Loeber, R., & Lahey, B. B. (2001). Which aspects of ADHD are associated with tobacco use in early adolescence? *J Child Psychol Psychiatry, 42,* 493-502.

Cardinal, R. N. (2006). Neural systems implicated in delayed and probabilistic reinforcement. *Neural Netw., 19,* 1277-1301.

Cardinal, R. N., Robbins, T. W., & Everitt, B. J. (2000a). The effects of d-amphetamine, chlordiazepoxide, alpha-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. *Psychopharmacology (Berl), 152,* 362-375.

Carlezon, W. A., Jr., Mague, S. D., & Andersen, S. L. (2003). Enduring behavioral effects of early exposure to methylphenidate in rats. *Biol.Psychiatry, 54,* 1330-1337.

Chartier, K. G., Hesselbrock, M. N., & Hesselbrock, V. M. (2010). Development and Vulnerability Factors in Adolescent Alcohol Use. *Child and Adolescent Psychiatric Clinics of North America, 19,* 493-+.

Chilcoat, H. D. & Breslau, N. (1999). Pathways from ADHD to early drug use. *J Am Acad Child Adolesc Psychiatry, 38,* 1347-1354.

Clark, D. B., Cornelius, J. R., Kirisci, L., & Tarter, R. E. (2005). Childhood risk categories for adolescent substance involvement: a general liability typology. *Drug Alcohol Depend., 77,* 13-21.

Clark, D. B., Moss, H. B., Kirisci, L., Mezzich, A. C., Miles, R., & Ott, P. (1997). Psychopathology in preadolescent sons of fathers with substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 36,* 495-502.

Clark, D. B., Thatcher, D. L., & Tapert, S. F. (2008). Alcohol, psychological dysregulation, and adolescent brain development. *Alcohol Clin Exp.Res, 32,* 375-385.

Coffey, S. F., Gudleski, G. D., Saladin, M. E., & Brady, K. T. (2003). Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. *Exp.Clin Psychopharmacol., 11,* 18-25.

Cohen, D. A. & Rice, J. (1997). Parenting styles, adolescent substance use, and academic achievement. *Journal of Drug Education, 27,* 199-211.

Compton, W. M., Thomas, Y. F., Stinson, F. S., & Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch.Gen.Psychiatry, 64,* 566-576.

Connor, D. F., Carlson, G. A., Chang, K. D., Daniolos, P. T., Ferziger, R., Findling, R. L. et al. (2006). Juvenile maladaptive aggression: A review of prevention, treatment, and service configuration and a proposed research agenda. *Journal of Clinical Psychiatry, 67,* 808-820.

Dalley, J. W., Fryer, T. D., Brichard, L., Robinson, E. S., Theobald, D. E., Laane, K. et al. (2007). Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science, 315,* 1267-1270.

Dalley, J. W., Laane, K., Pena, Y., Theobald, D. E., Everitt, B. J., & Robbins, T. W. (2005). Attentional and motivational deficits in rats withdrawn from intravenous self-administration of cocaine or heroin. *Psychopharmacology (Berl), 182,* 579-587.

Dalley, J. W., Mar, A. C., Economidou, D., & Robbins, T. W. (2008). Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. *Pharmacol.Biochem.Behav, 90,* 250-260.

de Wit, H., Enggasser, J. L., & Richards, J. B. (2002). Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology, 27,* 813-825.

Diaz, R., Goti, J., Garcia, M., Gual, A., Serrano, L., Gonzalez, L. et al. (2011). Patterns of substance use in adolescents attending a mental health department. *European Child & Adolescent Psychiatry, 20,* 279-289.

Dinges, M. M. & Oetting, E. R. (1993). Similarity in Drug-Use Patterns Between Adolescents and Their Friends. *Adolescence, 28,* 253-266.

Elkins, I. J., King, S. M., McGue, M., & Iacono, W. G. (2006). Personality traits and the development of nicotine, alcohol, and illicit drug disorders: prospective links from adolescence to young adulthood. *J Abnorm.Psychol, 115,* 26-39.

Elkins, I. J., McGue, M., & Iacono, W. G. (2007). Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Arch.Gen.Psychiatry, 64,* 1145-1152.

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology (Berl), 146,* 348-361.

Evenden, J. L. & Ryan, C. N. (1996). The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement. *Psychopharmacology (Berl), 128,* 161-170.

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2005). Show me the child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. *J Child Psychol Psychiatry, 46,* 837-849.

Fischer, M., Barkley, R. A., Edelbrock, C. S., & Smallish, L. (1990). The Adolescent Outcome of Hyperactive-Children Diagnosed by Research Criteria .2. Academic, Attentional, and Neuropsychological Status. *J Consult Clin Psychol, 58,* 580-588.

Flory, K. & Lynam, D. R. (2003). The relation between attention deficit hyperactivity disorder and substance abuse: what role does conduct disorder play? *Clin Child Fam.Psychol Rev., 6,* 1-16.

Galaif, E. R., Stein, J. A., Newcomb, M. D., & Bernstein, D. P. (2001). Gender differences in the prediction of problem alcohol use in adulthood: Exploring the influence of family factors and childhood maltreatment. *Journal of Studies on Alcohol, 62,* 486-493.

Gilman, S. E., Breslau, J., Conron, K. J., Koenen, K. C., Subramanian, S. V., & Zaslavsky, A. M. (2008a). Education and race-ethnicity differences in the lifetime risk of alcohol dependence. *J Epidemiol.Community Health, 62,* 224-230.

Gilman, S. E., Martin, L. T., Abrams, D. B., Kawachi, I., Kubzansky, L., Loucks, E. B. et al. (2008b). Educational attainment and cigarette smoking: a causal association? *Int J Epidemiol., 37,* 615-624.

Hasin, D. S., Stinson, F. S., Ogburn, E., & Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch.Gen.Psychiatry, 64,* 830-842.

Hawkins, J. D., Catalano, R. F., & Miller, J. Y. (1992a). Risk and Protective Factors for Alcohol and Other Drug Problems in Adolescence and Early Adulthood - Implications for Substance-Abuse Prevention. *Psychological Bulletin, 112,* 64-105.

Hawkins, J. D., Catalano, R. F., & Miller, J. Y. (1992b). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. *Psychol Bull., 112,* 64-105.

Hayatbakhsh, M. R., Mamun, A. A., Najman, J. M., O'Callaghan, M. J., Bor, W., & Alati, R. (2008). Early childhood predictors of early substance use and substance use disorders: prospective study. *Australian and New Zealand Journal of Psychiatry, 42,* 720-731.

Hayatbakhsh, M. R., Najman, J. M., Jamrozik, K., Al Mamun, A., Bor, W., & Alati, R. (2008). Adolescent problem behaviours predicting DSM-IV diagnoses of multiple substance use disorder. *Social Psychiatry and Psychiatric Epidemiology, 43,* 356-363.

Helms, C. M., Gubner, N. R., Wilhelm, C. J., Mitchell, S. H., & Grandy, D. K. (2008). D4 receptor deficiency in mice has limited effects on impulsivity and novelty seeking. *Pharmacol.Biochem.Behav., 90,* 387-393.

Hicks, B. M., Iacono, W. G., & McGue, M. (2010). Consequences of an Adolescent Onset and Persistent Course of Alcohol Dependence in Men: Adolescent Risk Factors and Adult Outcomes. *Alcoholism-Clinical and Experimental Research, 34,* 819-833.

Hser, Y. I., Evans, E., Huang, D., Brecht, M. L., & Li, L. (2008). Comparing the dynamic course of heroin, cocaine, and methamphetamine use over 10 years. *Addict.Behav, 33,* 1581-1589.

Hser, Y. I., Huang, D., Brecht, M. L., Li, L., & Evans, E. (2008). Contrasting trajectories of heroin, cocaine, and methamphetamine use. *J Addict.Dis., 27,* 13-21.

Imperato, A. & Di Chiara, G. (1986). Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. *J.Pharmacol.Exp.Ther., 239,* 219-228.

Isles, A. R., Humby, T., & Wilkinson, L. S. (2003). Measuring impulsivity in mice using a novel operant delayed reinforcement task: effects of behavioural manipulations and d-amphetamine. *Psychopharmacology (Berl), 170,* 376-382.

James, L. M. & Taylor, J. (2007). Impulsivity and negative emotionality associated with substance use problems and Cluster B personality in college students. *Addict.Behav, 32*, 714-727.

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2011). Marijuana use is rising; ecstasy use is beginning to rise; and alcohol use is declining among U.S. teens. Ref Type: Internet Communication

Kalivas, P. W. & Duffy, P. (1987). Sensitization to repeated morphine injection in the rat: possible involvement of A10 dopamine neurons. *J Pharmacol.Exp.Ther, 241,* 204-212.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P. et al. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry, 36,* 980-988.

Kirby, K. N., Petry, N. M., & Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp.Psychol Gen., 128*, 78-87.

Labouvie, E., Bates, M. E., & Pandina, R. J. (1997). Age of first use: its reliability and predictive utility. *J Stud.Alcohol, 58,* 638-643.

Lambert, N. M. & Hartsough, C. S. (1998). Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. *J Learn.Disabil., 31,* 533-544.

Lambert, N. M., Hartsough, C. S., Sassone, D., & Sandoval, J. (1987). Persistence of hyperactivity symptoms from childhood to adolescence and associated outcomes. *Am.J.Orthopsychiatry, 57,* 22-32.

Le Foll, B., Gallo, A., Le Strat, Y., Lu, L., & Gorwood, P. (2009). Genetics of dopamine receptors and drug addiction: a comprehensive review. *Behav.Pharmacol., 20,* 1-17.

Lee, S. S. & Hinshaw, S. P. (2006). Predictors of adolescent functioning in girls with attention deficit hyperactivity disorder (ADHD): The role of childhood ADHD, conduct problems, and peer status. *Journal of Clinical Child and Adolescent Psychology, 35,* 356-368.

Littlefield, A. K., Sher, K. J., & Steinley, D. (2010). Developmental Trajectories of Impulsivity and Their Association With Alcohol Use and Related Outcomes During Emerging and Young Adulthood I. *Alcoholism-Clinical and Experimental Research, 34,* 1409-1416.

Loney, J., Kramer, J. R., & Salisbury, H. (2002). Medicated versus unmedicated ADHD children: adult involvement with legal and illegal drugs. In P.S.Jensen & J. R.

Cooper (Eds.), *Attention deficit hyperactivity disorder: State of the science. Best practices* (pp. 17-1-17-16). Kingston, N.J.: Civic Research Institute.

Lynne-Landsman, S. D., Graber, J. A., Nichols, T. R., & Botvin, G. J. (2011). Trajectories of Aggression, Delinquency, and Substance Use Across Middle School Among Urban, Minority Adolescents. *Aggressive Behavior, 37,* 161-176.

Lynskey, M. T. & Fergusson, D. M. (1995). Childhood conduct problems, attention deficit behaviors, and adolescent alcohol, tobacco, and illicit drug use. *J Abnorm.Child Psychol, 23,* 281-302.

Madden, G. J., Bickel, W. K., & Jacobs, E. A. (1999). Discounting of delayed rewards in opioid-dependent outpatients: exponential or hyperbolic discounting functions?169. *Exp.Clin Psychopharmacol., 7,* 284-293.

Madden, G. J., Petry, N. M., Badger, G. J., & Bickel, W. K. (1997). Impulsive and self-control choices in opioid-dependent patients and non-drug-using control participants: drug and monetary rewards. *Exp.Clin Psychopharmacol., 5,* 256-262.

Mague, S. D., Andersen, S. L., & Carlezon, W. A., Jr. (2005). Early developmental exposure to methylphenidate reduces cocaine-induced potentiation of brain stimulation reward in rats. *Biol.Psychiatry, 57,* 120-125.

Mannuzza, S., Klein, R. G., Bessler, A., Malloy, P., & Hynes, M. E. (1997). Educational and occupational outcome of hyperactive boys grown up. *J Am Acad Child Adolesc Psychiatry, 36,* 1222-1227.

Mannuzza, S., Klein, R. G., Bessler, A., Malloy, P., & LaPadula, M. (1998). Adult psychiatric status of hyperactive boys grown up. *Am J Psychiatry, 155*, 493-498.

Mannuzza, S., Klein, R. G., Truong, N. L., Moulton, J. L., III, Roizen, E. R., Howell, K. H. et al. (2008). Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. *Am J Psychiatry, 165*, 604-609.

Martin, C. S., Lynch, K. G., Pollock, N. K., & Clark, D. B. (2000). Gender differences and similarities in the personality correlates of adolescent alcohol problems. *Psychology of Addictive Behaviors, 14*, 121-133.

Mayzer, R., Fitzgerald, H. E., & Zucker, R. A. (2009). Anticipating Problem Drinking Risk From Preschoolers' Antisocial Behavior: Evidence for a Common Delinquency-Related Diathesis Model. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*, 820-827.

Milberger, S., Biederman, J., Faraone, S. V., Chen, L., & Jones, J. (1997). ADHD is associated with early initiation of cigarette smoking in children and adolescents. *J Am Acad Child Adolesc Psychiatry, 36*, 37-44.

Miller, D. S. & Miller, T. Q. (1997). A test of socioeconomic status as a predictor of initial marijuana use. *Addictive Behaviors, 22*, 479-489.

Miller, G. A. & Chapman, J. P. (2001). Misunderstanding analysis of covariance. *J Abnorm.Psychol, 110*, 40-48.

Mischel, W., Shoda, Y., & Peake, P. K. (1988). The nature of adolescent competencies predicted by preschool delay of gratification. *J Pers Soc Psychol, 54,* 687-696.

Mitchell, J. M., Fields, H. L., D'Esposito, M., & Boettiger, C. A. (2005). Impulsive responding in alcoholics. *Alcohol Clin Exp.Res, 29,* 2158-2169.

Mitchell, S. H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology (Berl), 146,* 455-464.

Moffitt, T. E. (1993). Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychol Rev., 100,* 674-701.

Molina, B. S., Bukstein, O. G., & Lynch, K. G. (2002). Attention-deficit/hyperactivity disorder and conduct disorder symptomatology in adolescents with alcohol use disorder. *Psychol Addict.Behav, 16,* 161-164.

Molina, B. S. & Pelham, W. E., Jr. (2003). Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *J Abnorm.Psychol, 112,* 497-507.

Molina, B. S. G., Flory, K., Hinshaw, S. P., Greiner, A. R., Arnold, L. E., Swanson, J. M. et al. (2007). Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. *J Am Acad Child Adolesc Psychiatry, 46,* 1027-1039.

Molina, B. S. G., Pelham, W. E., Gnagy, E. M., Thompson, A. L., & Marshal, M. P. (2007). Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. *Alcoholism-Clinical and Experimental Research, 31,* 643-654.

Nako K & & Treas, J. (1994). Updating occupational prestige and socioeconomic scores: How the new measures measure up. *Sociol Methodol, 24,* 1-72.

Nestby, P., Schotte, A., Janssen, P. F., Tjon, G. H., Vanderschuren, L. J., De Vries, T. J. et al. (1997). Striatal dopamine receptors in rats displaying long-term behavioural sensitization to morphine. *Synapse, 27,* 262-265.

Paine, T. A., Dringenberg, H. C., & Olmstead, M. C. (2003). Effects of chronic cocaine on impulsivity: relation to cortical serotonin mechanisms. *Behav Brain Res, 147,* 135-147.

Pappadopulos, E., Jensen, P. S., Chait, A. R., Arnold, L. E., Swanson, J. M., Greenhill, L. L. et al. (2009). Medication adherence in the MTA: saliva methylphenidate samples versus parent report and mediating effect of concomitant behavioral treatment. *J Am Acad Child Adolesc Psychiatry, 48,* 501-510.

Pelham, W. E., Milich, R., Murphy, D. A., & Murphy, H. A. (1989). Normative Data on the Iowa Conners Teacher Rating-Scale. *Journal of Clinical Child Psychology, 18,* 259-262.

Perry, J. L., Larson, E. B., German, J. P., Madden, G. J., & Carroll, M. E. (2005). Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. *Psychopharmacology (Berl), 178,* 193-201.

Perry, J. L., Nelson, S. E., & Carroll, M. E. (2008). Impulsive choice as a predictor of acquisition of IV cocaine self- administration and reinstatement of cocaine-seeking behavior in male and female rats. *Exp.Clin Psychopharmacol., 16,* 165-177.

Petry, N. M. (2001). Delay discounting of money and alcohol in actively using alcoholics, currently abstinent alcoholics, and controls. 158. *Psychopharmacology (Berl), 154,* 243-250.

Pidoplichko, V. I., DeBiasi, M., Williams, J. T., & Dani, J. A. (1997). Nicotine activates and desensitizes midbrain dopamine neurons. *Nature, 390,* 401-404.

Poulos, C. X., Le, A. D., & Parker, J. L. (1995). Impulsivity predicts individual susceptibility to high levels of alcohol self-administration. *Behav Pharmacol., 6,* 810-814.

Pujazon-Zazik, M. & Park, M. J. (2009). Marijuana: Use Among Young Males and Health Outcomes. *American Journal of Mens Health, 3,* 265-274.

Ranaldi, R., Egan, J., Kest, K., Fein, M., & Delamater, A. R. (2009). Repeated heroin in rats produces locomotor sensitization and enhances appetitive Pavlovian and instrumental learning involving food reward. *Pharmacol.Biochem.Behav, 91,* 351-357.

Richards, J. B., Sabol, K. E., & de Wit, H. (1999). Effects of methamphetamine on the adjusting amount procedure, a model of impulsive behavior in rats. *Psychopharmacology (Berl), 146,* 432-439.

Roesch, M. R., Takahashi, Y., Gugsa, N., Bissonette, G. B., & Schoenbaum, G. (2007). Previous cocaine exposure makes rats hypersensitive to both delay and reward magnitude. 142. *J Neurosci., 27,* 245-250.

Rogers, G., Elston, J., Garside, R., Roome, C., Taylor, R., Younger, P. et al. (2009). The harmful health effects of recreational ecstasy: a systematic review of observational evidence. *Health Technology Assessment, 13,* 1-+.

Schempf, A. H. (2007). Illicit drug use and neonatal outcomes: A critical review. *Obstetrical & Gynecological Survey, 62,* 749-757.

Schubiner, H., Tzelepis, A., Milberger, S., Lockhart, N., Kruger, M., Kelley, B. J. et al. (2000). Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. *J Clin Psychiatry, 61,* 244-251.

Setlow, B., Mendez, I. A., Mitchell, M. R., & Simon, N. W. (2009). Effects of chronic administration of drugs of abuse on impulsive choice (delay discounting) in animal models. *Behav Pharmacol., 20,* 380-389.

Sher, K. J., Grekin, E. R., & Williams, N. A. (2005). The development of alcohol use disorders. *Annu.Rev.Clin Psychol, 1,* 493-523.

Sihvola, E., Rose, R. J., Dick, D. M., Pulkkinen, L., Marttunen, M., & Kaprio, J. (2008). Early-onset depressive disorders predict the use of addictive substances in adolescence: a prospective study of adolescent Finnish twins. *Addiction, 103,* 2045-2053.

Simon, N. W., Mendez, I. A., & Setlow, B. (2007). Cocaine exposure causes long-term increases in impulsive choice. *Behav Neurosci., 121*, 543-549.

Spanagel, R. & Shippenberg, T. S. (1993). Modulation of morphine-induced sensitization by endogenous kappa opioid systems in the rat. *Neurosci.Lett., 153,* 232-236.

Stalnaker, T. A., Takahashi, Y., Roesch, M. R., & Schoenbaum, G. (2009). Neural substrates of cognitive inflexibility after chronic cocaine exposure. *Neuropharmacology, 56*, 63-72.

Stanis, J. J., Marquez, A. H., White, M. D., & Gulley, J. M. (2008). Dissociation between long-lasting behavioral sensitization to amphetamine and impulsive choice in rats performing a delay-discounting task. *Psychopharmacology (Berl), 199*, 539-548.

Substance Abuse and Mental Health Services Administration (2010). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings*.

Sussman, S., McCuller, W. J., & Dent, C. W. (2003). The associations of social self-control, personality disorders, and demographics with drug use among high-risk youth. *Addict.Behav, 28,* 1159-1166.

Tarter, R., Vanyukov, M., Giancola, P., Dawes, M., Blackson, T., Mezzich, A. et al. (1999). Etiology of early age onset substance use disorder: A maturational perspective. *Development and Psychopathology, 11*, 657-683.

Tarter, R. E., Kirisci, L., Habeych, M., Reynolds, M., & Vanyukov, M. (2004). Neurobehavior disinhibition in childhood predisposes boys to substance use disorder by young adulthood: direct and mediated etiologic pathways. *Drug Alcohol Depend., 73,* 121-132.

Tarter, R. E., Kirisci, L., Mezzich, A., Cornelius, J. R., Pajer, K., Vanyukov, M. et al. (2003). Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *Am J Psychiatry, 160,* 1078-1085.

Tarter, R. E., Kirisci, L., Reynolds, M., & Mezzich, A. (2004). Neurobehavior disinhibition in childhood predicts suicide potential and substance use disorder by young adulthood. *Drug Alcohol Depend., 76 Suppl,* S45-S52.

Taylor, E., Chadwick, O., Heptinstall, E., & Danckaerts, M. (1996). Hyperactivity and conduct problems as risk factors for adolescent development. *J.Am.Acad.Child Adolesc.Psychiatry, 35,* 1213-1226.

Timmermans, M., van Lier, P. A., & Koot, H. M. (2008). Which forms of child/adolescent externalizing behaviors account for late adolescent risky sexual behavior and substance use? *J Child Psychol Psychiatry, 49,* 386-394.

Vanderschuren, L. J. & Kalivas, P. W. (2000). Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl), 151,* 99-120.

Vitale, S. & Van de Mheen, D. (2006). Illicit drug use and injuries: A review of emergency room studies. *Drug and Alcohol Dependence, 82*, 1-9.

Vuchinich, R. E. & Simpson, C. A. (1998). Hyperbolic temporal discounting in social drinkers and problem drinkers. 155. *Exp.Clin Psychopharmacol., 6,* 292-305.

Wade, T. R., de Wit, H., & Richards, J. B. (2000). Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. *Psychopharmacology (Berl), 150,* 90-101.

Wang, B., You, Z. B., Rice, K. C., & Wise, R. A. (2007). Stress-induced relapse to cocaine seeking: roles for the CRF(2) receptor and CRF-binding protein in the ventral tegmental area of the rat. *Psychopharmacology (Berl), 193,* 283-294.

Waschbusch, D. A. (2002). A meta-analytic examination of comorbid hyperactive-impulsive-attention problems and conduct problems. *Psychol Bull., 128,* 118-150.

Wilhelm, C. J. & Mitchell, S. H. (2008). Rats bred for high alcohol drinking are more sensitive to delayed and probabilistic outcomes. *Genes Brain Behav, 7,* 705-713.

Winstanley, C. A., LaPlant, Q., Theobald, D. E., Green, T. A., Bachtell, R. K., Perrotti, L. I. et al. (2007). DeltaFosB induction in orbitofrontal cortex mediates tolerance to cocaine-induced cognitive dysfunction. 141. *J Neurosci., 27,* 10497-10507.

Wise, R. A. (2000b). Addiction becomes a brain disease. *Neuron, 26*, 27-33.

Wise, R. A. (2000). Interactions between medial prefrontal cortex and meso-limbic components of brain reward circuitry. *Prog.Brain Res., 126,* 255-262.

Wise, R. A. (2004). Dopamine and food reward: back to the elements. *Am.J.Physiol Regul.Integr.Comp Physiol, 286,* R13.

Wise, R. A. (2005). Forebrain substrates of reward and motivation. *J.Comp Neurol., 493,* 115-121.

Wise, R. A. & Bozarth, M. A. (1987). A psychomotor stimulant theory of addiction. *Psychol Rev., 94,* 469-492.

You, Z. B., Wang, B., Zitzman, D., Azari, S., & Wise, R. A. (2007). A role for conditioned ventral tegmental glutamate release in cocaine seeking. *J.Neurosci., 27,* 10546-10555.

Zimmermann, P., Wittchen, H. U., Hofler, M., Pfister, H., Kessler, R. C., & Lieb, R. (2003). Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychol Med., 33,* 1211-1222.

Zucker, R. A., Donovan, J. E., Masten, A. S., Mattson, M. E., & Moss, H. B. (2008). Early developmental processes and the continuity of risk for underage drinking and problem drinking. *Pediatrics, 121 Suppl 4,* S252-S272.