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Subjective responses to initial experience with cocaine: an exploration of the incentive–sensitization theory of drug abuse

Nadine M. Lambert[1], Marsha McLeod[1] & Susan Schenk[2]

University of California at Berkeley, Berkeley, CA, USA[1] and Victoria University of Wellington, New Zealand[2]

ABSTRACT

Aims This study investigated the relationship between positive and negative subjective responses at the time of initial cocaine use with adult cocaine dependence and life-time use rates. Psychostimulant pre-exposure, regular smoking or stimulant treatment before initiation were examined to explore the incentive sensitization theory of addiction. **Participants** A total of 202 adult participants who had tried cocaine on at least one occasion were studied prospectively from childhood into adulthood. The cocaine-initiated group included 89 who met *Diagnostic and Statistical Manual* version IV (DSM-IV) criteria for attention deficit hyperactive disorder (ADHD) and 113 age-matched controls. **Design** Five childhood and three adulthood interviews provided data on ages of initiation into cocaine and life-time use of cocaine from ages 16–40 years. Correlations of each subjective response and analyses of variance (ANOVAs) of cocaine 'liking' and 'wanting' with DSM-III-R cocaine dependence and life-time use provided support for the validity of the measures. ANOVA provided evidence of the effect of psychostimulant pre-exposure on 'liking' and 'wanting'. Logistic regression modeled the prediction of dependence and life-time use with the independent variables of 'liking' and 'wanting', psychostimulant pre-exposure and participant characteristics. **Results** When cocaine was first tried, 'liking' and 'wanting' were significant predictors of cocaine dependence and life-time use. Mean 'liking' or 'wanting' responses did not differ by participant characteristics. Those who were pre-exposed by regular smoking or stimulant treatment had higher 'liking' and 'wanting' scores; but participants who were pre-exposed by both stimulant treatment and regular smoking reported the lowest liking and the highest wanting responses, consistent with the incentive sensitization theory. Logistic regression showed that the 'liking' and 'wanting' responses increased significantly the odds of DSM-III-R cocaine dependence and life-time use. **Conclusion** In this sample, subjective 'liking' and 'wanting' measured risk for cocaine abuse.

Keywords ADHD, cocaine dependence, incentive–sensitization theory, life-time use of cocaine, stimulant treatment, subjective responses to cocaine, tobacco smoking.

Correspondence to: Nadine M. Lambert, Graduate School of Education, Cognition and Development, University of California at Berkeley, Berkeley, CA 94720–1670, USA. E-mail: nlambert@socrates.berkeley.edu
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BACKGROUND

Drugs with high abuse liability, such as cocaine, produce both positive and negative effects (Lowenstein *et al.* 1987) that influence both the initiation and continued use of these drugs. For those not initiated into cocaine, Schafer & Brown (1991) showed that expectations of negative effects were a deterrent to initial use and expectations of positive effects were shown to be associated with initiation into and continued use of the drug. Positive effects, such as euphoria or liking, have been demonstrated (Haertzen 1966; Hill *et al.* 1963; Haertzen, Hill & Belleville 1966) for many abused drugs and the magnitude of these positive effects experienced during first use of cocaine was correlated with continued use of cocaine (Davidson, Finch & Schenk 1993). Positive effects, however, appear less important to the maintenance of drug-taking by experienced users (Fischman *et al.* 1985), while wanting or craving a drug has been shown to be related to continued self-administration of the drug and to the development of drug abuse (Foltin & Fischman 1991a).

In humans, a great deal of evidence on subjective responses to cocaine has been derived from studies using the long and short forms of the Addiction Research

Center Inventory (ARCI; Haertzen 1966; Haertzen *et al.* 1966; Foltin & Fischman 1991b). Cocaine users reported higher levels of subjective responses to items reflecting euphoria and social effectiveness (MBG scale), positive mood (A scale) and having a sense of control (BG scale). The contribution of craving to drug taking has been measured by examining the relationship between responses to questions such as 'I want', 'I need' or 'I crave' and drug use. Craving was elicited by prior exposure to cocaine as well as to cues that had been associated with cocaine self-administration (Ehrman *et al.* 1992; Grant *et al.* 1996; Childress *et al.* 1999; Bonson *et al.* 2002; Weiss *et al.* 2003; Jaffe *et al.* 1989). These findings suggest that for experienced users, craving for cocaine is likely to lead to cocaine-seeking and cocaine-taking, thereby initiating a compulsive cycle of drug-seeking and drug-taking that characterizes abuse and differentiates it from use. Further, the magnitude of craving might be a good indicator of abuse potential in users who have not yet become abusers. Schafer & Brown (1991) developed subjective response scales based on self-reports of individuals not initiated into cocaine to measure the expected effects of cocaine. They identified five domains of expectancies labeled global positive effects, global negative effects, generalized arousal, anxiety and relaxation and tension reduction. The items on their global positive scale were comparable to items on the MBG, A and BG ARCI scales. Their global negative scale included a 'craving' item, 'always wanted more'.

Davidson *et al.* (1993) used the Schafer & Brown scales to evaluate the relationship between positive and negative subjective responses and subsequent cocaine use among relatively inexperienced college students. The magnitude of the 'liking' or positive effects reported for first use of cocaine was correlated positively with life-time use of the drug and correlated negatively with latency to second use of cocaine. The only negative cocaine effect that was correlated significantly with subsequent use was one that reflected cocaine-craving. Thus, in this sample of relatively young college students who had not used cocaine extensively, both cocaine-liking and cocaine-wanting were correlated positively with indices of continued cocaine use.

Robinson and Berridge's (1993, 2000, 2003) and Berridge and Robinson's (1995) 'incentive–sensitization theory' accounts for the psychological and neurobiological basis of drug craving leading to dependence. According to this theory, pleasure is the first stage of incentive motivation and serves to activate mechanisms of associative learning and incentive salience. Incentive salience of a drug results, in part, from pleasurable experience with the drug and the environmental contexts in which the drug is used. When the pleasurable effects of drugs become reduced with repeated exposure, compulsive drug-seeking may occur as a result of sensitization of those brain systems that are normally involved with incentive motivation and reward. Sensitization of these brain systems is hypothesized to mediate the incentive salience of the drug ('wanting') as opposed to the pleasurable or euphoric effects of the drugs ('liking') and to explain, in part, why an individual may still 'crave' the drug even though the pleasurable effects of the drug are reduced.

Evidence of sensitization in humans is limited, probably because of ethical limitations that constrain the ability to administer drugs repeatedly with high abuse liability. Pre-clinical studies have, however, demonstrated consistently sensitization to many behavioral and neurochemical effects of drugs of abuse following repeated exposure (Lett 1989; Piazza *et al.* 1989; Horger, Shelton & Schenk 1990; Shippenberg & Heidbreder 1995; Pierre & Vezina 1997; Vezina 2004).

In animal studies pre-exposure to nicotine and other psychostimulants, such as caffeine and methylphenidate, sensitized laboratory animals to the effects of cocaine (Horger, Giles & Schenk 1992; Brandon *et al.* 2001; Schenk & Izenwasser 2002). Sensitization might explain why the use of so-called gateway drugs such as nicotine increases the risk of subsequent drug use (Kandel & Yamaguchi 1993; Kandel, Yamaguchi & Chen 1992; Schenk 2002).

The incentive–sensitization theory proposes that compulsive drug use exhibited by abusers is determined primarily by sensitized drug-wanting. If so, measurement of drug-liking and drug-wanting after initiation into cocaine might be diagnostic tools for identifying high-risk individuals. The present study examined this hypothesis by correlating retrospective reports of initial experiences of liking or wanting cocaine with the incidence of cocaine dependence and rates of life-time use among adults who had been initiated into cocaine. The participants were older than those in the Davidson *et al.* (1993) study; a large percentage met *Diagnostic and Statistical Manual* version III—revised (DSM-III-R) criteria for cocaine dependence and many had high rates of life-time use of cocaine. The sample was therefore suited to examination of factors that contribute to heavy use and dependence.

The incentive–sensitization theory also predicts that a history of psychostimulant exposure sensitizes drug-wanting systems, thereby increasing the risk for subsequent abuse. In this study some participants were treated with stimulants and/or were regular smokers prior to cocaine initiation and there were some who were not regular smokers nor treated with stimulants. Rates of dependence and life-time use of these groups were developed to evaluate the association between psychostimulant pre-exposure to cocaine dependence and life-time use.

In studies of risk factors for cocaine abuse, one must account for the effects of participant characteristics.

Research by the authors has shown that childhood attention deficit hyperactive disorder (ADHD) and stimulant treatment are related significantly to rates of tobacco use and DSM-III-R tobacco dependence and cocaine dependence (Hartsough & Lambert 1987; Lambert & Hartsough 1998; Lambert 2002). Initiation to and use of tobacco as well as other illicit drugs may have common determinants in psychosocial unconventionality, such as aggressiveness and conduct disorders (Loney 1980; Jessor & Jessor 1980; Kellam, Ensminger & Simon 1980; Robins 1980); however, no hypotheses are offered to state that ADHD or problem behavior affect subjective responses to cocaine when it is first tried.

METHOD

Participants

The 202 cocaine-initiated adult participants were among 399 adults born from 1962 to 1968 from a community sample of 492 children who were identified in a study of the prevalence of hyperactivity (the diagnostic term predating ADHD) in the 1973–74 school year (Lambert, Sandoval & Sassone 1978, 1979). These subjects continued to participate in a prospective longitudinal investigation of the life histories of ADHD and age-matched control participants. The adult participants were characteristic of the original sample with respect to socio-economic status, gender, criminal histories and ADHD status (Hartsough, Babinski & Lambert 1996). The representative sample of children from a demographically diverse area for the prevalence estimates were selected by sampling randomly 40 classrooms each at grade: from kindergarten to grade 5 from all the public, private and parochial schools in Alameda and Contra Costa Counties in the East Bay Region of the San Francisco Metropolitan Area. District and school consent to participate followed the random selection. Identification of hyperactive/ADHD participants in 233 representative classrooms involved referrals from three recruitment sources—parents, teachers and local treating physicians. Teachers identified any child who had hyperactive symptoms, any who were being treated for hyperactivity or any who had been referred for medical evaluation. We then interviewed each parent and requested consent for the physician evaluation. The Alameda Contra Costa County Medical Association supported the research by asking physicians to refer children in the selected schools who were being evaluated or treated for hyperactivity. A team of child medical specialist consultants assisted us in developing a standard medical evaluation and diagnostic form (Lambert *et al*. 1979). Details about the selection methods, parent consent procedures and results have been described elsewhere (Lambert, Sandoval & Sassone 1978, 1979; Lambert 2002). The identification procedures were comparable to those used by other investigators in follow-up studies (Borland & Hechtman 1976; Satterfield, Hoppe & Schell 1982; Mannuzza *et al*. 2003; MTA Cooperative Group 1999). For the purpose of the prevalence estimates, a child was identified as hyperactive if all three identification systems were in concurrence.

Supplementing the procedures for estimating the prevalence of hyperactivity, we developed parent and teacher rating scales, the Children's Attention and Adjustment Survey (CAAS) (Lambert, Sandoval & Hartsough 1990), with items selected from the research literature that distinguished hyperactive from non-hyperactive children and behaviors that were sensitive to stimulant medication. Parental consent was available for teacher ratings of 5212 children. Factor analyses of these scales resulted in four factor scales—inattention, impulsitivity, hyperactivity and conduct problems—and provided baseline assessment of what were later to be specified as the cardinal symptoms of ADHD. The diagnostic proxy for ADHD based on the CAAS parent and teacher ratings showed excellent reliabilities from 0.87 to 0.94 (Lambert & Hartsough 1987; Lambert *et al*. 1990).

We identified two age-matched control groups. The first were any additional children in each classroom whose total CAAS teacher ratings were at the 96th percentile or higher, the range of ratings assigned to the children identified by the teachers, parents and physicians. Parental consent was then sought for an interview. If a child did not meet the research diagnostic criteria for hyperactivity following the parent interview, he or she became a member of a fourth group, 'the behavior controls'. A second age-matched control group was composed of children of the same age and gender in the classroom of a hyperactive child with no current presenting symptoms. If there was more than one matching child, the age-matched control was selected randomly. Parents consented to their child's participation in the research as control participants. Even though we found an age-match in the same classroom as the hyperactive child, parental consent resulted in differences in the total number of hyperactive children and age-matched controls. The original sample was composed of 492 participants, among whom were 214 diagnosed and treated hyperactive child participants, 68 who met the identification criteria but were untreated hyperactive controls, 59 behavior problem controls and 159 age-matched controls for a total of 492 children who, with parental permission, became the sample for the longitudinal effort. There were 108 females and 114 members of ethnic minority groups among the total sample. Although some of the participants may have tried a cigarette, none of them was a regular smoker at the time that they were identified.

Each subsequent year we followed the longitudinal sample to interview the parents and the participants themselves, providing an ongoing record of health, academic, social, behavioral status and substance use, as well as medical and treatment interventions. Parental consent was available for 340 of the 492 participants over the developmental period. Participants were interviewed five times from the onset of the study until the end of high school. When we began the adult data collection, we were no longer restricted to parent consent for participation. We attempted, therefore, to locate all the original 492 subjects and were successful in finding and interviewing 399 adults (81%) of the original sample of 492 at an average age of 26. Fifteen (3%) had died and 28 (6%) refused to participate These adult participants were interviewed at two later occasions and these data, combined with those collected during late childhood and high school, provided a comprehensive record of the age of initiation and life-time use of licit and illicit substances at a particular age until age 40 years.

Procedures

The first adult interview was administered when the subjects were an average age of 26 years. The interview included the Schafer & Brown subjective response questionnaire and eight major sections guided by other long-term studies describing the developmental course of educational, social, health, mental health outcomes, tobacco and substance use and driving and criminal histories (Ahlgren *et al.* 1982; Werner 1989, 1991; Swan, Murray & Jarrett 1991; Hawkins, Catalano & Miller 1992). The interview also included the Quick Diagnostic Interview Schedule III—Royal (QDSM-III-R) (Marcus, Robins & Bucholz 1990) that provided diagnoses of the major mental disorders and psychoactive substance use disorders. The second and third adult interviews included employment and educational information, health and family histories, as well as substance use reports.

Several approaches to uncovering evidence of response bias in reports of drug use and criminal activity were explored. Child and adolescent reports of use of a particular substance were compared with reports as adults regarding the age at which they first tried tobacco, cocaine and other substances. There was a remarkable consistency in these reports, such as agreement between an adult report of the age regular smoking began with childhood interview data that they were involved in smoking at that age. Babinski *et al.* (2001) reported kappa coefficients that reflected considerable concordance between self-reported measures of criminal involvement and official arrest records for a sample that included these participants. Based on the evidence available, the agreement between self-reported drug use measures over time and between self-reports and measures from other sources for this sample of participants is likely to be sufficiently high to provide reliable measures for this investigation.

Independent variables in the analyses

ADHD status

Among the 202 cocaine-initiated participants were 89 who met research diagnostic criteria for DSM-IV ADHD (American Psychiatric Association 1994). The diagnostic proxy was CAAS ratings above a numerical threshold on the inattentive or hyperactive–impulsive scales. By applying these criteria to the entire sample we were able to establish a contemporary classification of the participants as ADHD or not ADHD. CAAS ratings were available from both parents and teachers, thus satisfying the symptom threshold and multiple settings requirements. Evidence for significant impairment before age 7 came from parent reports of age of onset on the symptoms, reports of the age they first sought medical intervention or of early childhood temperament, such as a high activity level and problems in attention and persistence (Lambert 1982). Medical reports from physicians at baseline for all potential ADHD children allowed for detection of any disorders demanding exclusion of the ADHD diagnosis. Participants were classified as ADHD if the symptoms were pervasive (both home and school ratings in the criterion range) or situational (either a home or school rating in the criterion range) and if they met the other diagnostic criteria. The remainder of the participants was classified as not-ADHD. Eighty-nine per cent of the initial hyperactive group and 9% of the control groups satisfied the DSM-IV ADHD diagnostic criteria. Those in the control group who satisfied the diagnostic criteria with ratings above the threshold on the CAAS inattention scale might have been identified as ADHD if diagnostic criteria and reliable measures of them had been available in 1974. Among those who met the research diagnostic criteria for DSM-IV ADHD, 56% had been treated with stimulants, and 9% of those with subthreshold ratings on the ADHD criteria had received stimulant treatment.

Childhood problem behavior

The criteria for childhood conduct problems/aggressiveness was an average rating of 2.5 or higher on the conduct problem scale from the home and school versions of the CAAS. Participants were classified as 'severe conduct problems' if both parent and teacher ratings were in the criterion range, as 'moderate conduct problems' if only one rating was in the criterion range, and no qualifying ratings as 'no conduct problems'.

A measure of early onset childhood conduct disorders was derived from participant self-reports at the end of high school of the number of times they had committed acts against people or property, were deceitful or reported rule

violations consistent with the DSM-IV criteria for conduct disorders. Any participant who subscribed to at least one conduct disorder criterion was classified as early onset conduct disorders. Among these participants, 87% never reported any conduct disorder behavior before age 12.

Psychostimulant exposure prior to cocaine initiation

Treatment histories were obtained contemporaneously during the childhood years and into adulthood. We documented the age when stimulant treatment was started, the number of years it was used and the age when treatment ended. The stimulant treatment data are not retrospective, therefore, but are true reports of each participant's stimulant medication history. Among those treated with stimulants, 65% were treated with methylphenidate, 20% with methylphenidate plus another stimulant and 15% received dexedrine, benzedrine, Cylert or Deaner. In all cases first cocaine use occurred after treatment had been terminated.

The records of tobacco use were derived from childhood, adolescent and adult interviews (Lambert & Hartsough 1998). Table 1 shows the number of cocaine-initiated participants from age 3 to older than 20 who were initiated into tobacco, the ages at which they became regular smokers, the ages of first stimulant treatment, the age when stimulant treatment ended and the age of initiation into cocaine.

Participants were divided into four groups that reflected stimulant treatment and/or nicotine exposure prior to cocaine use: (1) stimulant treatment and regular smoking (19%); (2) stimulant treatment only (14%); (3) regular smoking only (25%); and (4) neither stimulant treatment or regular smoking (26%). An additional 16% of the participants became regular smokers after they were initiated into cocaine and data from these subjects were therefore not considered in the analysis of the effects of psychostimulant pre-exposure on the subjective responses.

Subjective response to cocaine upon initiation

The subjective response items on the Schafer & Brown scale reflect positive 'liking' and negative responses (including 'wanting') after cocaine was first tried. An analysis of the relationship of the items to DSM-III-R cocaine dependence and life-time use of cocaine provided the basis for selecting the subjective response measures to be used in the investigation.

Dependent variables in the investigation

Cocaine dependence

The first interview administered when the participants were an average age of 26 included the QDIS-III-R (Marcus *et al*. 1990) that provided DSM-III-R (American Psychiatric Association 1987) diagnoses of the psychoactive substance use disorders as well as diagnoses of the major mental disorders. Comparisons between the computer-administered interview and clinician-administered interviews (Erdman *et al*. 1992) show consistency in diagnoses across methods and studies of the stability (Vandiver & Sher 1991) and retest reliability (Ross *et al*. 1995) reveal good reliabilities across methods over time. Among those initiated into cocaine, 77 (38%) of them satisfied the DSM-III-R criteria for cocaine dependence at the time of the first interview. It needs to be noted that if the DSM diagnoses of substance use disorders were obtained during the second and third interviews, some additional cases might have met this criterion.

Life-time use of cocaine

The cocaine use data included the age at which participants reported they had been initiated into cocaine and their reports of life-time use using the Center for Disease Control (CDC) continuum of use (CDC 1999). The average age of initiation into cocaine for these participants was 17.2 years. The data from the interviews from the onset of the study to the end of high school and three consecutive adult interviews provided estimates of life-time use of cocaine at five age periods from ages 16–20 to 36–40 years. Our reviews of the reports of life-time use at these age levels indicated that cocaine use increased until age 26, after which it leveled off. For this investigation we used life-time use rates at ages 26–30 and 36–40.

Table 1 Ages of initiation into tobacco, regular smoking and cocaine and ages of stimulant treatment, $n = 202$.

	Age groups					
Type of psychostimulant exposure	*Not applicable*	*3–10*	*11–13*	*14–16*	*17–19*	*20+*
First tried tobacco	6	71	65	44	13	3
Initiated regular smoking	70	11	24	46	28	23
First stimulant treatment	136	62	4	0	0	0
Last stimulant treatment	136	31	25	9	1	0
First tried cocaine	0	1	10	75	85	31

Among those with a diagnosis of cocaine dependence, 61% reported a life-time use of cocaine that was greater than 40 times.

Data analysis procedures

Initially, the relationships between the subjective responses to the measures of cocaine dependence and life-time use were ascertained. The items from the Schafer & Brown scale were correlated with DSM-III-R cocaine dependence and life-time use of cocaine at ages 26–30 and 36–40. ANOVA provided evidence of the significance relationship of the subjective responses to DSM-III-R cocaine dependence and life-time use at 26–30 and 36–40.

χ^2 analysis was used to evaluate the association between psychostimulant exposure and the dependent variables of cocaine dependence and life-time use of cocaine at 26–30 and 36–40. Differences in subjective responses for the four psychostimulant pre-exposure groups were computed using one-way ANOVA.

To evaluate the magnitude of the effects of ADHD, problem behavior and gender, logistic regression analyses provided estimates of the extent to which each of these independent participant variables increased the odds of cocaine dependence at an average age of 26 and life-time use of cocaine at ages 26–30 and 36–40 when the other independent variables of participant characteristics, psychostimulant pre-exposure and the subjective responses of 'liking' and 'wanting' were accounted for.

RESULTS

The relationship of 'liking' and 'wanting' to cocaine dependence and life-time use

The first step in the analysis of the subjective responses was to explore their psychometric properties. This was accomplished by conducting a factor analysis of the items to determine whether the data for this sample replicated the findings reported by Schafer & Brown. Two factors were identified reflecting a positive and a negative response scale. Table 2 reports the correlation of the subjective responses with the cocaine measures. All the positive items and three of the negative items ('always wanted more', 'hallucinations' and 'worse judgement') had significant positive correlation with the cocaine measures. Among all the items the 'wanting' item had the highest correlation with cocaine dependence and life-time use. The 'liking' measure for this research was composed as a sum of the positive items, and the 'wanting' measure as the value of the item 'always wanted more'. The reliability of the positive or 'liking' scale was 0.91 and the correlation between the 'liking' scale and the 'wanting' item was 0.29.

The mean 'liking' and 'wanting' responses and the significance of the one-way ANOVA with η^2 for DSM-III-R cocaine-dependent versus not-dependent participants, and for those with different levels of life-time use for age groups from 16 to 40 are shown in Table 3. Participants in the 16–20 and 21–25 age groups were fairly inexperienced in cocaine use. The frequency of using cocaine

Table 2 Correlations of positive and negative responses with DSM-III-R cocaine dependence and life-time use of cocaine at two age periods.

Items	*Cocaine dependence*	*Life-time use*	
		26–30 years	*36–40 years*
Positive subjective responses			
Conversation more interesting	0.21**	0.22**	0.23**
Euphoric	0.23**	0.28***	0.26**
Get more done	0.24**	0.24**	0.27***
On top of things	0.24**	0.28***	0.25***
Could do anything	0.29***	0.31***	0.27***
Sociable	0.20**	0.28***	0.29***
More happy	0.15*	0.21**	0.24***
Thought more clearly	0.22**	0.21**	0.21**
Negative subjective responses			
Shaky	0.19**	0.15*	0.13
Thoughts not deep	0.06	0.12	0.13
Decreased sexual performance	0.01	0.11	0.04
Always wanted more	0.41***	0.32***	0.35***
Hallucinations	0.30***	0.13	0.12
Worse judgement	0.27***	0.25***	0.22**
Fearful	0.15*	0.10	0.08

*$P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.

Table 3 Mean cocaine abuse liability score for DSM-III-R cocaine dependent and not dependent, and for life-time use rates at ages 16–40.

DSM-III-R cocaine dependence and life-time use	n^1	*'Liking'*			*'Wanting'*		
		M	*SD*	*F*; η^2	*M*	*SD*	*F*; η^2
DSM-III-R psychoactive substance use disorder				9.81; 0.05**			47.64; 0.19***
Not dependent	144	18.47	6.36		2.35	1.07	
Cocaine-dependent	55	21.64	6.41		3.44	0.78	
Life-time use 16–20				NS			NS
Initiated	127	10.53	6.59		2.69	1.12	
Experimenter	43	18.81	6.03		2.44	1.08	
40+ times	11	20.55	5.61		3.27	1.10	
Life-time use 21–25				NS			6.58; 0.06**
Initiated	110	19.32	6.87		2.69	1.14	
Experimenter	64	18.68	5.78		2.40	1.04	
40+ times	27	21.33	6.46		3.30	0.91	
Life-time use 26–30				11.39; 0.10***			12.31; 0.11***
Initiated	27	16.04	7.40		2.07	1.13	
Experimenter	100	18.41	6.04		2.49	1.06	
40+ times	74	21.91	5.86		3.09	1.0	
Life-time use 31–35				12.42; 0.11***			15.75; 0.13***
Initiated	20	15.90	7.53		2.05	1.09	
Experimenter	94	17.89	6.33		2.37	1.06	
40 + times	88	21.74	5.58		3.10	0.99	
Life-time use 36–40				10.97; 0.10***			14.73; 0.13***
Initiated	18	16.28	7.71		2.10	1.12	
Experimenter	95	17.85	6.34		2.35	1.07	
40+ times	89	21.62	5.66		3.09	0.99	

**$P \leq 0.01$; *** $P \leq 0.001$. [1]When the total number of subjects in an age group does not equal 202, the total number in the sample who were initiated into cocaine, the value reported reflects the number who had been initiated into cocaine by that age period.

more than 40 times shows a progression from age 16 to 25, after which the rates level off. Both 'liking' and 'wanting' measures are significantly higher for the cocaine-dependent participants at an average age of 26, and higher for those who reported life-time use of more than 40 + times at ages 26–30 to 36–40.

'Liking' and 'wanting' responses by gender, ADHD and childhood problem behavior

With the exception of gender, with females having lower 'wanting' scores, there were no significant differences between mean 'liking' and 'wanting' responses for the ADHD and not-ADHD groups, the groups defined by severe, moderate and no conduct problems, or those with early onset of conduct disorders compared with no early onset of conduct disorders.

'Liking' and 'wanting' responses for those with differing psychostimulant histories prior to cocaine initiation

Ages of exposure to psychostimulants

Table 4 reports the mean ages of stimulant treatment, ages of initiation into tobacco and cocaine and ages of becoming a regular smoker for the psychostimulant exposure groups. These data indicate that tobacco and stimulant pre-exposed participants were initiated into tobacco earlier, were initiated into cocaine at an earlier age and were regular smokers at a younger age than the other groups. They also terminated stimulant treatment at an earlier age. Those who were exposed to stimulant treatment and who were not regular smokers terminated treatment later, their treatment lasted longer and they were initiated into cocaine later than those who were exposed only by regular tobacco smoking. These data suggest an 'exposure' effect resulting from the age initiated into tobacco and age when stimulants were first prescribed and the amount and length of exposure of these psychostimulants that needs further exploration.

Psychostimulant pre-exposure and cocaine dependence and life-time use

The significance of the χ^2 assessing the relationship between psychostimulant pre-exposure and cocaine dependence and life-time use are reported in Table 5. The rates of dependence and life-time use are highest for the

Table 4 Mean ages of exposure to psychostimulants for groups with different psychostimulant histories prior to cocaine initiation.

	Psychostimulant pre-exposure			
	Regular smoking and stimulant treatment n = 38	*Stimulant treatment only n = 28*	*Regular smoking only n = 51*	*Neither regular smoking nor stimulant treatment n = 52*
First stimulant treatment	7.1	6.9	NA	NA
Last stimulant treatment	10.3	10.7	NA	NA
Average number of years of stimulant treatment	3.1	3.7	NA	NA
Tobacco initiation	11.1	13.4	11.2	12.4
Regular smoking	13.6	NA	14.4	NA
Cocaine initiation	16.5	17.8	17.1	17.9

Table 5 Percentage of DSM-III-R cocaine dependence and rates of life-time use of cocaine for groups with different psychostimulant histories prior to cocaine initiation.

	Psychostimulant pre-exposure				
	Regular smoking and stimulant treatment n = 38	*Stimulant treatment only n = 28*	*Regular smoking only n = 51*	*Neither regular smoking nor stimulant treatment n = 52*	χ^2, *d.f.* = 3
Cocaine-dependent	47.4	33.3	33.3	5.9	Pearson = 20.48
Not cocaine-dependent	52.6	66.7	66.7	94.1	Likelihood ratio = 23.81, $P \leq 0.001$
Life-time use ages 26–30					
40+ times	50.0	35.7	39.2	19.2	Pearson = 10.76
3–39 times	42.1	46.4	49.0	61.6	Likelihood ratio = 11.25,
1–2 times	7.9	17.9	11.8	19.2	$P \leq 0.10$
Life-time use ages 36–40					
40+ times	52.6	46.4	47.1	25.0	Pearson = 10.99
3–39 times	42.1	35.7	43.1	67.3	Likelihood ratio = 11.22,
1–2 times	5.3	17.9	9.8	7.7	$P \leq 0.05$

regular smoking and stimulant treatment groups, about the same for either the regular smoking or the stimulant treatment groups and lowest for the group with no psychostimulant pre-exposure. It should be noted that the stimulant-only group was being treated until a later age, began smoking regularly at a later age and tried cocaine at ages older than the other groups. Psychostimulant exposure before cocaine initiation therefore is associated with significantly higher rates of DSM-III-R cocaine dependence and life-time use.

Figure 1 displays the standard score means of the 'liking' and 'wanting' responses for the four psychostimulant pre-exposure groups. The ANOVA for the 'liking' score by the psychostimulant exposure groups was not significant; however, those with both stimulant and tobacco pre-exposure had the lowest average scores.

Psychostimulant pre-exposure groups differed on the 'wanting' item ($F = 2.127$, $\eta^2 = 0.117$, $P \leq 0.05$) The contrasts showed that the stimulant and tobacco pre-exposure group had significantly higher mean scores for 'wanting' than the group with no psychostimulant exposure consistent with the predictions of Robinson & Berridge. There were no significant differences between the regular smoking and the stimulant treatment groups, but the means of these groups were significantly different from the means of those with no psychostimulant pre-exposure.

One might conclude from the data on Fig. 1 that the low endorsement of 'liking' responses among the group with both stimulant and tobacco pre-exposure would be reflected in lower rates of cocaine dependence and life-time use. But the results show the reverse of this prediction—the rates of cocaine dependence and life-time use of cocaine are highest for participants with both stimulant and tobacco pre-exposure, those subjects with the lowest 'liking' responses. To explore this further, we computed

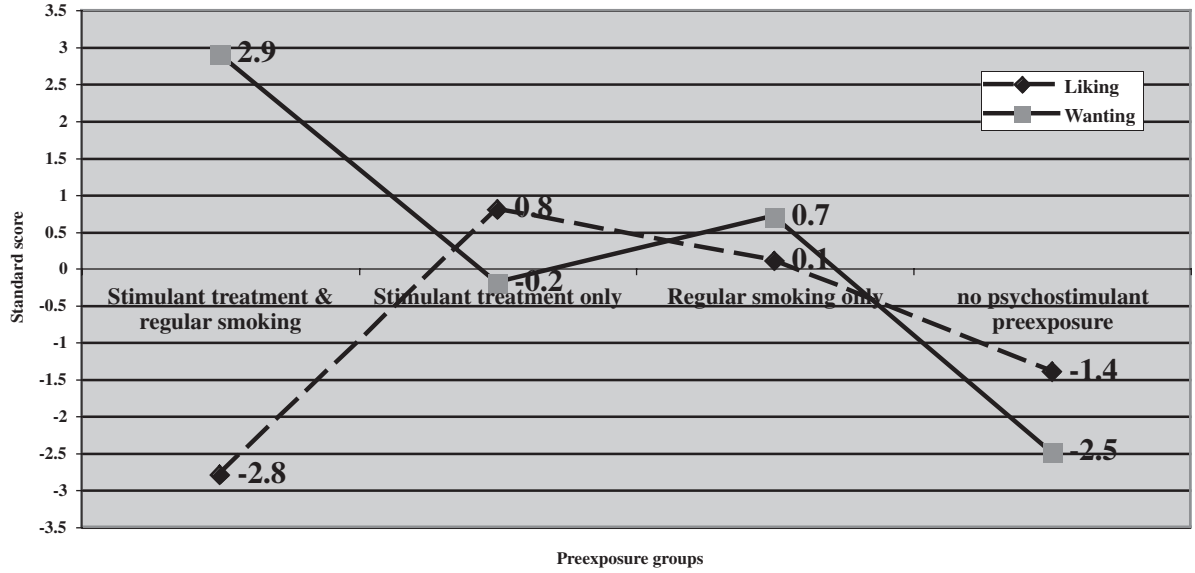

Figure 1 'Liking' and 'wanting' measures for psychostimulant pre-exposure groups

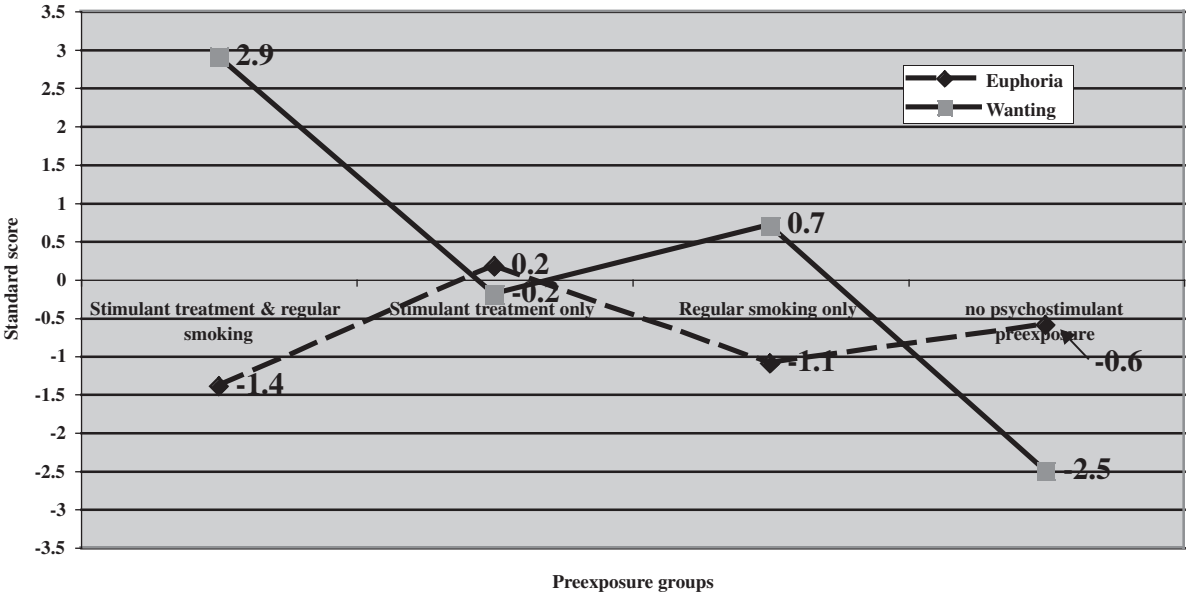

Figure 2 'Euphoria' and 'wanting' measures for psychostimulant exposure groups

the means for the psychostimulant exposure groups for the 'euphoria' response in the 'liking' scale because an experience of euphoria would reflect most closely an experience of pleasure and hedonic reactions to the first experience with cocaine. Figure 2 displays the mean standard scores for the 'euphoria' item and shows the same pattern of responses: those with both stimulant treatment and regular tobacco smoking before cocaine initiation reported the lowest 'euphoria' responses and the highest 'wanting' responses.

The logistic regression modeling the independent variables of gender, ADHD, conduct problems, regular smoking and stimulant treatment before cocaine initiation and the 'liking' and 'wanting' measures in the prediction of the dependent variables of DSM-III-R cocaine dependence and life-time use at ages 26–30 and 36–40 were then explored (see Table 6). With the exception of gender, the variables in the model for ages 26–30 with significant coefficients and adjusted odds ratios greater than 1.0, taking into account the standard error, predicting DSM-III-R cocaine dependence were ADHD, regular smoking before cocaine initiation, stimulant treatment, and the 'liking' and 'wanting' abuse liability measures. The variables in the model predicting life-time use at ages

Table 6 Models for predicting DSM-III-R cocaine dependence and life-time cocaine use at ages 26–30 and 36–40.

	Cocaine dependence and life-time use		
Variables in the the analysis	*DSM-III-R cocaine dependence Adjusted OR*	*Life-time use at 26–30 Adjusted OR*	*Life-time use at 36–40 Adjusted OR*
Participant characteristics			
Gender	2.359	2.140^{+}	1.991
DSM-IV ADHD diagnostic proxy	1.456*	1.017	0.994
Conduct problems-aggressiveness	0.296**	0.515*	0.722
Psychostimulant exposure before cocine initition			
Regular smoking	3.120**	1.947^{+}	1.500
Stimulant treatment	1.756*	1.416	1.271
Subjective responses at time of cocaine initiation			
'Liking'	1.090*	1.110***	1.103***
'Wanting'	3.362***	1.669**	1.786***

$^{+}P \leq 0.10$; $^{*}P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$.

26–30 and 36–40 with significance levels of $P \leq 0.05$ and adjusted odds ratios greater than 1.0 were the 'liking' and 'wanting' abuse liability measures.

DISCUSSION

Participants who were cocaine-dependent at an average age of 26 or who were heavy users at ages 26–40, irrespective of psychostimulant pre-exposure, reported higher levels of 'liking' cocaine by endorsing items that were like those in the MBG, A and BG scales of the ARCI measuring euphoria, positive mood and intellectual efficiency and energy. Additionally, those who were cocaine-dependent or were heavy cocaine users reported 'wanting' cocaine significantly more than those who were not dependent or were only experimental cocaine users.

Attempts to explain differences in the propensity to abuse cocaine have focused on sensitization following exposure to psychostimulants. We examined the relationship between psychostimulant exposure and liking and wanting responses by measuring effects as a function of experience with smoking and stimulant treatment. Consistent with the theory, the stimulant and tobacco pre-exposure group reported the lowest 'liking' scores when they first tried cocaine, but they reported significantly higher 'wanting' responses than the group that was not pre-exposed. Both 'liking' and 'wanting' responses for those with either stimulant treatment or regular tobacco smoking were higher than those reported by the not pre-exposed group. This result is consistent with the predictions of Robinson & Berridge and psychopharmacological evidence showing that repeated exposure to stimulants (stimulant treatment and regular smoking) may reduce the pleasurable effects of the later use of the stimulant, cocaine and, in turn, would be reflected in lower endorsement of 'liking' responses.

The χ^2 analyses of psychostimulant history with DSM-III-R cocaine dependence ($P \leq 0.001$) and life-time use at age 26–30 and 36–40 differed ($P \leq 0.08$ and $P \leq 0.05$). The strength of the association with life-time use increased as the participants became older and more of them reported higher levels of use. Those with exposure to either regular smoking or stimulant treatment had similar rates of cocaine dependence and life-time use. The lowest rates of dependence and life-time use were associated with no psychostimulant pre-exposure. These results support the idea that psychostimulant pre-exposure by stimulant treatment and regular tobacco smoking, consistent with psychopharmacological research, may sensitize relevant systems to cocaine.

The models predicting DSM-III-R cocaine dependence and life-time use at 26–30 and 36–40 showed that ADHD increased the odds of cocaine dependence, but not life-time use. The criteria for DSM-III-R diagnosis of psychoactive substance dependence requires evidence that the individual continues to use the substance despite the presence of psychological, social, occupational or health problems and the person is aware that these problems may be exacerbated by the use of the substance. Those with ADHD may be considered to be compromised in the ability to control or self-regulate the impulse to use substances and to become dependent on them.

When the variable 'childhood conduct problems' was introduced into the logistic regressions, this was significant for cocaine dependence and life-time use at ages 26–30, but the odds ratios were only 0.296 and 0.515, respectively. It is important to note that among those who

met the criteria for childhood conduct problems are those who would be considered to have DSM-IV 'early onset conduct disorders' in adolescence, those whose problems were transient and did not persist into adolescence and those with no evidence of problem behavior in childhood. Among the latter group are those participants who did not meet the criteria for childhood conduct problems but developed conduct disorders in adolescence, or those that would be classified as a DSM-IV 'late onset conduct disorder' group. These results therefore do not address questions about whether conduct disorders in adolescence, both early and late, affect a diagnosis of cocaine dependence or life-time use.

One might conclude from the data on Fig. 1 that the low endorsement of 'liking' responses among the group with both stimulant and tobacco pre-exposure would be reflected in lower rates of cocaine dependence and life-time use. The argument might follow that stimulant treatment and smoking could serve as 'protective' factors for cocaine abuse as Biederman *et al.* (1999) have suggested. However, the results show the reverse of this prediction—the rates of cocaine dependence and life-time use of cocaine are highest for participants with both stimulant and tobacco pre-exposure, those subjects with the lowest 'liking' responses.

These data on human participants extend the incentive–sensitization theory that proposes that pleasure from or liking the effects of a drug is the first stage of incentive motivation and serves to activate mechanisms of associative learning and incentive salience. With repeated exposure the pleasurable effects of drugs become reduced, and compulsive drug seeking may result from sensitization of those brain systems that are normally involved with incentive motivation and reward. Robinson & Berridge hypothesize that sensitization of these brain systems mediates the incentive salience of the drug ('wanting') as opposed to the pleasurable or euphoric effects of the drugs ('liking') and explains, in part, why an individual may still 'crave' the drug even though the pleasurable effects of the drug are diminished.

The prospective life-history longitudinal records came from a community sample of participants followed from early childhood to early adulthood. Limits to this study should be noted. It was not possible to obtain the subjective responses at the time of cocaine initiation contemporaneously. Many years had elapsed between the age of initiation into cocaine and the reports of subjective responses. Controlled laboratory methods were not feasible with this community population. We cannot rule out these data because they were retrospective, however. Those who were cocaine-dependent might endorse more craving responses, but they would not be expected to account for psychostimulant pre-exposure, in reporting their 'liking' or 'euphoria' responses.

Some potentially important findings about psychostimulant pre-exposure emerged from this study. The data suggest that answers to important questions about stimulant pre-exposure should be sought regarding the timing of the stimulant treatment and the onset of regular smoking. Recent reports (Andersen *et al.* 2001; Brandon *et al.* 2001) suggest that the age and duration of stimulant exposure must be accounted for. The average age of and length of stimulant treatment varied for participants in psychostimulant pre-exposure groups under study. Further, there was a wide range of ages when participants became regular smokers. Robins & Pryzbeck (1985) reported that beginning drug use before 15 years of age increased the risk of drug disorders, and initiation into tobacco at 11 years of age or earlier reported by Lambert (2002) was associated with dependence and life-time use of tobacco and cocaine and other substances.

Although there were significant differences supporting the objectives of the study with small effect sizes, it must be noted that the sample size of 202 cocaine-initiated participants may have restricted the power to detect differences other than those reported.

The results reported for effects of psychostimulant pre-exposure, however, are in line with the extensive psychopharmacological evidence from animal research that shows an association between psychostimulant pre-exposure and sensitization and self-administration of cocaine. Exploration of the relationship of 'wanting' (sensitization) to latency between initiation and regular use of cocaine could extend the findings of Horger, Giles & Schenk (1992), Horger, Shelton & Schenk (1990), Pierre & Vezina (1997) and Schenk & Partridge (2000). Measures of cocaine abuse liability derived from scales assessing subjective responses of 'liking' and 'wanting' cocaine when it is first used may be useful measures of vulnerability to cocaine abuse and addiction.

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