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Adolescent Cannabis Use Increases Risk for Cocaine-Induced Paranoia

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Abstract

Cannabis can produce and/or exacerbate psychotic symptoms in vulnerable individuals. Early exposure to cannabis, particularly in combination with genetic factors, increases the risk of a subsequent, primary, psychotic disorder. Because paranoia is a common feature of stimulant abuse and cocaine dependent individuals frequently endorse a history of cannabis abuse, we examined whether early cannabis exposure, in conjunction with polymorphic variation in the catechol-O-methyl transferase gene (*COMT* Val158Met), influences the risk for cocaine-induced paranoia (CIP).

Methods—Cannabis-use history was obtained in 1140 cocaine-dependent individuals from a family-based (affected sibling pair) study using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). Logistic regression and generalized estimating equations analyses were used to examine the role of adolescent-onset cannabis use (≤ 15 yrs of age) on CIP risk, both controlling for previously implicated CIP risk factors and familial relationships, and considering potential interactions with *COMT* Val158Met genotype.

Results—Cocaine-dependent individuals who endorsed CIP had significantly higher rates of adolescent-onset cannabis use than those without CIP (62.2% vs. 50.2%; $\chi^2 = 15.2$, $df = 1$, $p < 0.0001$), a finding that remained after controlling for sibling correlations and other risk factors. There were

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Conflict of Interest We declare that there are no conflicts of interest related to the work.

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no effects of *COMT* genotype or genotype by early cannabis onset interactions. A modest ($OR = 1.4$) and nearly significant ($p = 0.053$) effect of CIP status in probands on CIP status in siblings was also noted.

Conclusions—Adolescent-onset cannabis use increases the risk of CIP in cocaine dependent individuals. *COMT* genotype and its interaction with early cannabis exposure did not emerge as significant predictors of CIP. In addition, trait vulnerability to CIP may also be familial in nature.

Keywords

cocaine; paranoia; cannabis; adolescent

1. Introduction

Paranoia, a distrust of others or fear of being harmed (Satel et al., 1991), is experienced by 50 – 80% of cocaine-dependent individuals (Brady et al., 1991; Satel et al., 1991; Rosse et al., 1994; Bartlett et al., 1997; Cubells et al., 2005; Kalayasiri et al., 2006a). Both demographic and cocaine-use-related risk factors for cocaine-induced paranoia (CIP) have been previously reported (Brady et al., 1991; Cubells et al., 2005; Floyd et al., 2006; Kalayasiri et al., 2006a). To our knowledge, however, interactions with other psychoactive agents, including cannabis, have yet to be explored. Given the high rates of co-occurring cannabis use among chronic cocaine users (Miller et al., 1990; Aharonovich et al., 2006), and recent evidence supporting a role for early-onset cannabis use in the risk for primary psychotic disorders, we examined whether marijuana use is associated with the risk for CIP.

According to the 2007 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2008), 40.6% of all Americans ages 12 or older had tried cannabis at least once. Of greater concern, the rate of exposure among teens (12–17 year olds) was 16.2%. The latter statistic is especially alarming in the context of recent evidence that early-onset cannabis use may be associated with an increased risk for primary psychotic disorder (Arseneault et al., 2004; Degenhardt and Hall, 2006; Fergusson et al., 2006b; Hall, 2006; Linszen and van Amelsvoort, 2007). In a longitudinal birth cohort study, Caspi and colleagues (2005) found evidence of a gene by environment interaction in which adolescent cannabis users carrying “Val”, the high-activity allele, at the Val158Met polymorphism in the gene encoding catechol-O-methyl transferase (*COMT*) were more vulnerable to subsequent development of psychosis (Caspi et al., 2005; Henquet et al., 2006). These findings were consistent with some prior studies showing associations between polymorphic variation in *COMT* and schizophrenia-related phenotypes (Egan et al., 2001; Bilder et al., 2002; Shifman et al., 2002; Wonodi et al., 2003), although recent meta-analyses have not supported such associations for schizophrenia (Glatt et al., 2003; Fan et al., 2005; Munafo et al., 2005; Okochi et al., 2009).

Despite an awareness of the high prevalence of cannabis use among primary cocaine users (i.e., 50–70%) (Miller et al., 1990; Aharonovich et al., 2006), an appreciation of cocaine’s paranoia-producing capacity (Addiction Research Center (NIDA); Sherer et al., 1988; Muntaner et al., 1989; Sughondhabirrom et al., 2005; Kalayasiri et al., 2006b; Kalayasiri et al., 2007), and knowledge that cannabis produces and/or influences the risk of psychotic symptom development, we found no published studies examining potential relationships between cannabis exposure and CIP. Thus, we studied a large sample of cocaine-dependent individuals in the context of a family (i.e., affected sibling pair linkage) study, to evaluate potential interactions between cannabis and cocaine use, including gene (*COMT* Val158Met) by environment (adolescent cannabis exposure) interaction.

2. Methods

The study sample consisted of 1140 cocaine-dependent individuals who participated in a large, collaborative, family-based (affected sibling pair), multi-site study on the genetics of cocaine and opioid dependence (Gelernter et al., 2005; Gelernter et al., 2006), 840 of whom have been reported on previously (Kalayasiri et al., 2006a). Diagnostic, demographic, and drug use data were obtained using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) (Pierucci-Lagha et al., 2005; Pierucci-Lagha et al., 2007). Subjects provided blood or saliva for the isolation of DNA and genetic analysis. Individuals were genetically categorized as European American (EA) or African American (AA) by a short tandem repeat linkage marker set (Gelernter et al., 2005) using the Structure program (Pritchard et al., 2000). Subjects provided full, written, informed consent prior to their participation, and the research was approved by the appropriate institutional review boards at each of the collaborating sites (Yale University School of Medicine; University of Connecticut Health Center; McLean Hospital; Medical University of South Carolina; Boston University). Prior to their analysis, non-normally distributed SSADDA data were log transformed (e.g., age of first cocaine use). If still non-normally distributed, the data were then categorized (e.g., daily amounts and severity of cocaine dependence/DSM-IV symptom count), as previously described (Kalayasiri et al., 2006a). Per prior studies (Caspi et al., 2005), we defined adolescent-onset cannabis exposure as an episode of first use at age 15 or younger.

As in our prior work (Gelernter et al., 1994; Cubells et al., 2000; Gelernter et al., 2005; Kalayasiri et al., 2006a), CIP was defined by positive responses to each of the following two questions: 1) “Have you ever had a paranoid experience?” and 2) “Have you ever had a paranoid experience while using cocaine?” (Satel et al., 1991). Per the SSADDA, these questions were preceded by a standardized, written, investigational definition of “paranoia” (“an intense fear that you will be caught or harmed in some way when you know that these things cannot happen”), as well as specific examples (e.g., “the idea that a noise at a fourth floor window means someone is there, or that a shadow behind a door means someone is crouching there”).

Subjects were genotyped at rs4680, a functional, single-nucleotide polymorphism (SNP) in *COMT* located at codon 158, using a Taqman assay, at Yale. Hardy-Weinberg Equilibrium Expectations (HWE) were tested using Genetic Data Analysis (GDA) with 10,000 simulations. Genotypes were assayed in duplicate. For statistical analyses, a set of dummy codes were applied to *COMT* genotypes (Val/Val = 0, Val/Met = 1, Met/Met = 2) and cannabis onset (adolescent onset = 0, other = 1). Gene by environment interactions were defined and analyzed as the multiplied product of the two respective codes (described below).

To control for correlated variables, factors associated with CIP were first identified in the total sample, as previously described (Kalayasiri et al., 2006a). In brief, demographic, cocaine use, and diagnostic variables were compared among individuals with and without CIP using a two-tailed chi-square or independent sample t-test. Variables that were significantly associated with CIP in the initial analysis were tested by forward logistic regression analysis to confirm the effect. Variables that were highly correlated (defined as Bonferroni corrected $p < 0.005$) with the statistically most robust variable were dropped at each step of the model. After identifying potential risk factors for CIP, we performed a primary logistic regression analysis by including in the model the effects of adolescent cannabis onset, *COMT* genotype, and their interaction on CIP status (as noted above). CIP risk factors identified as significant during initial analyses were included in the logistic regression to control for their effects on cannabis, *COMT*, and interaction effects. In addition, methods identical to those described above were performed to assess for the effects of adolescent-onset use, genotype, and their interaction on CIP status in EA and AA subpopulations (both by analyses of potential three-way interactions and by two-way interactions for each respective / separate subpopulation).

Generalized estimating equation (GEE) analysis of the association between CIP and adolescent cannabis onset, and CIP and *COMT* genotype, was also performed to control for the influence of sibling relationships in the sample. We fitted logistic regression models with family as the clustering factor and an exchangeable working correlation matrix within family. We started with a model in which adolescent cannabis onset, genotype, and proband or sibling status were fixed factors, and considered all possible interactions among these factors. Non-significant effects were dropped by backwards elimination to obtain the best-formulated model. Variables found to be risk factors for CIP were treated as covariates in the analysis. Finally, potential familial influences on the risk for CIP were investigated by studying the effect of CIP status in probands on that in siblings using logistic regression analyses. The model controlled for potential effects of environmental risk factors (e.g., severity of cocaine dependence, age of cocaine onset, and propensity of probands' CIP status from these environmental risks) as described previously (Kalayasiri et al., 2006a).

3. Results

3.1) Demographic, cocaine use, and diagnostic variables and risk for CIP

Of 1140 cocaine dependent subjects, 738 (64.7%) endorsed CIP. Age ($t = -2.0$, $df = 1138$, $p = 0.048$), and race (EAs; $\chi^2 = 4.1$, $df = 1$, $p = 0.04$), but not sex ($\chi^2 = 1.6$, $df = 1$, $p = 0.20$) distinguished individuals with CIP (age, 38.3 ± 7.5 yrs) from those not endorsing CIP (age, 39.2 ± 7.1 yrs) (Table 1). In addition, several cocaine use characteristics emerged as initially associated with CIP, including daily amount of money spent during periods of heaviest use ($\chi^2 = 24.7$, $df = 3$, $p < 0.0001$), cocaine smoking ($\chi^2 = 13.1$, $df = 1$, $p = 0.0003$), snorting ($\chi^2 = 11.1$, $df = 1$, $p = 0.001$), and injection ($\chi^2 = 5.2$, $df = 1$, $p = 0.02$), earlier age of first use (20.4 ± 5.8 vs. 21.7 ± 6.2 years; $t = -3.7$, $df = 1138$, $p = 0.0002$), and severity of cocaine dependence as measured by DSM-IV symptom count ($\chi^2 = 36.7$, $df = 1$, $p < 0.0001$). Similarly, diagnoses of alcohol dependence ($\chi^2 = 10.8$, $df = 1$, $p = 0.001$), cannabis dependence ($\chi^2 = 11.1$, $df = 1$, $p = 0.001$), and sedative dependence ($\chi^2 = 7.0$, $df = 1$, $p = 0.008$) were also associated with the presence of CIP (two-tailed chi-square test or independent sample t-test; Table 1). Following logistic regression analysis, however, only the DSM-IV symptom count (dependence severity; OR = 2.1, $p < 0.0001$) and earlier age of onset of cocaine use (OR = 6.4, $p = 0.001$) remained as significant risks for CIP. Other initially associated variables were dropped from the model due to their high correlation ($p < 0.005$) with these statistically more robust ones.

3.2) Cannabis onset, interaction by *COMT* genotype, and CIP familiarity

CIP-positive, cocaine dependent individuals had a significantly higher rate of adolescent-onset (≤ 15 yrs) cannabis use than those without CIP (62.2% vs. 50.2%; $\chi^2 = 15.2$, $df = 1$, $p < 0.0001$). In contrast, cocaine-dependent individuals with CIP did not differ from those without CIP with respect to *COMT* genotype ($\chi^2 = 0.1$, $df = 2$, $p = 0.95$) or allele frequencies ($\chi^2 = 0.03$, $df = 1$, $p = 0.87$) (Table 2). When onset of cannabis use, *COMT* genotype, and their interaction were analyzed concurrently using logistic regression, adolescent-onset cannabis use was the only factor to emerge as significant (OR = 1.6, $p = 0.02$) (Table 3). There was a trend for this to be significant (OR = 1.5, $p = 0.06$) when the severity of cocaine dependence (DSM-IV symptom count) was controlled for in the model (age of onset of cocaine use was removed from the model due to its strong correlation with the more robust variable, adolescent cannabis onset). Similarly, there was no difference in CIP vulnerability with respect to *COMT* genotype or allele frequencies in either AA ($\chi^2 = 0.2$, $df = 2$, $p = 0.90$; $\chi^2 = 0.2$, $df = 1$, $p = 0.64$) or EA populations ($\chi^2 = 0.3$, $df = 2$, $p = 0.88$; $\chi^2 = 0.03$, $df = 1$, $p = 0.87$) (Table 2). Neither were significant interactions of *COMT* genotype with adolescent cannabis onset found in our logistic regression analysis, whether by combined three-way analyses (OR = 0.8, $p = 0.74$) or by subpopulation specific two-way analyses (AA, OR = 0.7, $p = 0.53$; EA, OR = 0.9, $p = 0.83$). The distribution

of *COMT* genotypes in the total sample were in HWEE ($p = 0.17$) as tested by GDA (10,000 simulations).

Significant influences of adolescent-onset cannabis use on CIP were reproduced after accounting for potential correlations between affected siblings by GEE analysis (with family as the clustering factor) ($\chi^2 = 14.7$, $df = 1$, $p = 0.0001$). This finding remained when controlling for severity of cocaine dependence in the model ($\chi^2 = 11.38$, $df = 1$, $p = 0.0007$; Table 4). Effects of genotype, and genotype by cannabis interactions, were not significant, and were dropped from the final model. Interestingly, an effect of familiarity (i.e., the influence of proband CIP status on that in siblings) was nearly significant ($OR = 1.4$, $p = 0.053$) by logistic regression analysis after controlling for both severity of cocaine dependence and age of cocaine onset.

4. Discussion

To our knowledge, this is the first study to report on the association between early onset cannabis use and risk for CIP. Our results are consistent with prior reports suggesting similar influences of early onset cannabis use on the vulnerability to idiopathic / primary psychosis (Arseneault et al., 2004; Caspi et al., 2005; Degenhardt and Hall, 2006; Fergusson et al., 2006b; Hall, 2006; Linszen and van Amelsvoort, 2007). Cannabis effects on CIP were robust and statistically discernable after considering and controlling for other known risk factors (e.g., younger age at onset of cocaine use; cocaine dependence severity) (Brady et al., 1991; Cubells et al., 2005; Floyd et al., 2006; Kalayasiri et al., 2006a). In contrast, we found no evidence of an effect of *COMT* genotype or genotype by cannabis interaction with respect to CIP risk. Intriguingly, however, we note a potential familial effect on CIP trait vulnerability in the context of our sibling data.

Delta-9-tetrahydrocannabinol (THC), a pharmacologically and behaviorally active compound found in cannabis, is known to produce transient psychotic experiences in healthy human subjects (D'Souza et al., 2004) and can exacerbate psychotic symptoms in vulnerable (e.g., schizophrenic) individuals following acute administration (D'Souza et al., 2005). However, risk for CIP in our cohort was not associated with either current (CIP vs. non-CIP; 33.1% vs. 31.6%; $\chi^2 = 0.3$, $df = 1$, $p = 0.61$) or lifetime cannabis use (CIP vs. non-CIP; 94.4% vs. 91.5%; $\chi^2 = 3.6$, $df = 1$, $p = 0.06$). Rather, influences on paranoia vulnerability only emerged when adolescent-onset cannabis use was considered. As such, our results suggest that cannabis has a neurodevelopmental role, whereby early exposure, perhaps during critical periods of brain maturation, sets the stage for subsequent paranoia risk (e.g., after exposure to cocaine). This hypothesis is supported by longitudinal studies of psychosis vulnerability in cohorts prospectively evaluated for early onset cannabis use (Caspi et al., 2005).

Although neurobiological mechanisms whereby early cannabis exposure might influence paranoia / psychosis / CIP vulnerability are unknown, THC-induced alterations in mesolimbic / mesocortical dopaminergic neurotransmission are one possibility (Tanda et al., 1997; Linszen and van Amelsvoort, 2007). Cocaine and other psychostimulants are believed to produce psychotic symptoms by increasing cortical and subcortical dopamine levels. Thus, cannabis might have a "sensitizing" effect on brain dopamine systems, one that predisposes individuals to CIP vulnerability. Such effects, if present, might be indirect, as $D_{2/3}$ receptor antagonists (e.g., haloperidol) fail to block psychotic symptoms associated with acute THC administration (D'Souza et al., 2008).

Interestingly, early onset cocaine use has been previously shown to be a risk factor for CIP, both by our group (Kalayasiri et al., 2006a) and others (Cubells et al., 2005; Floyd et al., 2006). Although this variable remained significant in our expanded cohort, analyses also

demonstrated a strong and statistically significant correlation between early onset of cocaine use and early onset of cannabis use, a finding consistent with reports that marijuana use is a “gateway” for other drugs of abuse (Kandel, 1975; Fergusson and Horwood, 2000; Agrawal et al., 2004; Fergusson et al., 2006a; Kandel et al., 2006) but that could equally well be explained by shared genetic vulnerability for these two forms of substance dependence with different ages of onset. In fact, in our final models, the effect of adolescent cannabis exposure was statistically more robust than that for early cocaine use with respect to CIP risk, raising the possibility that prior findings may have been accounted for, either in whole or in part, by early cannabis use. However, we cannot exclude the possibility that early onset cocaine and/or cannabis use are proxies for a latent psychosis vulnerability phenotype. In fact, some have pointed to potentially shared neurobiological determinants of the comorbid vulnerability to psychotic and substance use disorders (Chambers et al., 2001).

As noted above, we failed to find an effect of *COMT* genotype and/or cannabis/*COMT* interactions on CIP vulnerability, whether in our combined sample or separately by population (i.e., EA or AA). This is in contrast to some (Caspi et al., 2005), but not all studies (Zammit et al., 2007) of diverse primary psychotic symptoms. Several factors could underlie our negative results, including differences in phenotype (drug-induced vs. primary psychosis) or ascertainment (epidemiologic vs. clinical), statistical (type 2) error, and/or genetic factors (e.g., *COMT* variants other than Val158Met or *COMT* haplotypes may explain prior association findings). In addition, our findings of familiarity as a potential risk factor for CIP in the current expanded cohort (i.e., one that nonetheless included a smaller subset of individuals in whom no familial influence was found) (Kalayasiri et al., 2006a) merits further study, particularly in light of recent positive reports of genetic associations (e.g., MANEA) with the trait (Farrer et al., 2009). Future studies that focus on expanded phenotypes (e.g., cocaine and/or primary psychosis, or even aspects of cognitive function, in addition to paranoia), larger samples (including those in more extended families), and/or more detailed / fine-grained genetic (e.g., haplotypic) analyses, may ultimately be helpful in more definitively answering these questions.

Finally, and in contrast to prior longitudinal studies (Caspi et al., 2005), our cross-sectional design precludes drawing conclusions regarding a causal relationship between adolescent cannabis onset and CIP. Despite the use of a rigorous, prospectively defined, and previously validated phenotypic assessment, detailed information on the age of CIP onset was lacking. This would have been very difficult to determine retrospectively. Moreover, lack of association in an exclusively cocaine dependent population does not exclude the possibility that cannabis may influence CIP in non-dependent populations. Future studies (whether cross-sectional or longitudinal) that carefully focus on the temporal chronology of the two phenomena are warranted. That being said, the fact that the mean age of cocaine onset in our sample was in the early 20's, while the criteria used for adolescent cannabis onset was 15 yrs or younger (Caspi et al., 2005), provides indirect support that adolescent cannabis use predisposes to the subsequent occurrence of CIP in our sample. These results provide the first concrete evidence of a clinical relationship between early cannabis use and drug- (i.e., cocaine-) induced psychotic symptoms (i.e., paranoia). Our findings have important implications for the future study of the pathophysiology of psychosis vulnerability and, perhaps, public mental health interventions that focus on adolescents as a target group for the prevention of etiologically diverse psychotic symptoms.

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Table 1

Demographic, diagnostic, and cocaine use characteristics of cocaine-dependent individuals with and without cocaine-induced paranoia (CIP)

	Paranoid (N = 738)		Non-paranoid (N=402)		p-Value
	n	%	n	%	
Sex					
Male	376	50.9	189	47.0	0.20
Female	362	49.1	213	53.0	
Race					
European American (EA)	349	47.3	165	41.0	0.04 ^a
African American (AA)	389	52.7	237	59.0	
Tobacco dependence	526	71.3	275	68.4	0.31
Alcohol dependence	389	52.7	171	42.5	0.001 ^a
Opiate dependence	343	46.5	171	42.5	0.20
Cannabis dependence	254	34.4	100	24.9	0.001 ^a
Sedative dependence	74	10.0	22	5.5	0.008 ^a
Stimulant dependence	61	8.3	26	6.5	0.28
Times cocaine used in lifetime					
Do not know	86	11.7	44	10.9	0.76
>2000	380	51.5	201	50.0	
1–2000	272	36.9	157	39.1	
Daily money spent for cocaine (US\$) during period of heaviest use					
Do not know	82	11.1	37	9.2	<0.0001 ^a
≥100	470	63.8	223	55.5	
50–99	123	16.7	69	17.2	
1–49	62	8.4	73	18.2	
Dependence severity (DSM-IV symptom count)					
6–7	540	73.3	223	55.6	<0.0001 ^a
3–5	197	26.7	178	44.4	
Cocaine smoking	632	87.1	312	78.8	0.0003 ^a
Cocaine nasal use	592	81.5	289	73.0	0.001 ^a

	Paranoid (N = 738)		Non-paranoid (N=402)		p-Value
	n	%	n	%	
Cocaine injection	244	33.6	107	27.0	0.02 ^a

^aTwo-tailed χ^2 test.

Table 2

Genotypes				Alleles			
	Val/Val	Val/Met	Met/Met	p-Values	Val	Met	p-Values
Total (N = 1140)							
Paranoid (N, %)	293	39.7%	334	45.3%	111	15.0%	0.95
Non-paranoid (N, %)	163	40.5%	178	44.3%	61	15.2%	0.95
EA (N = 514)							
Paranoid (N, %)	91	26.1%	177	50.7%	81	23.2%	0.88
Non-paranoid (N, %)	44	26.7%	80	48.5%	41	24.8%	0.88
AA (N = 626)							
Paranoid (N, %)	202	51.9%	157	40.4%	30	7.7%	0.90
Non-paranoid (N, %)	119	50.2%	98	41.4%	20	8.4%	0.90

Table 3

Logistic regression analysis of the effects of *COMT* Val158Met genotype, adolescent-onset cannabis use, and their interaction on cocaine-induced paranoia

	ORs	p-Values	95% Confidence interval	
			Lower	Upper
Adolescent-onset cannabis use	1.6	0.02 ^a	1.1	2.3
<i>COMT</i> Val158Met genotypes				
Val/Val	1.1	0.69	0.7	1.8
Val/Met	1.2	0.43	0.7	2.0
Met/Met	-	-	-	-
G x E interaction ^b	0.7	0.31	0.3	1.4

^a Compared to non-adolescent onset of cannabis use and no exposure to cannabis.

^b Gene (e.g., *COMT* Val158Met) by environment (e.g., adolescent-onset cannabis use) interaction was derived from calculation product of dummy codes that were assigned to *COMT* genotype status (i.e., 0 = Val/Val, 1 = Val/Met, 2 = Met/Met) and onset of cannabis use (i.e., 0 = adolescent onset, 1 = others). Statistics is shown for the calculation product equals 0, compared to the calculation product equals 2.

Table 4

Generalized Estimating Equations (GEE) analysis of the association between cocaine-induced paranoia and adolescent cannabis use in 1140 cocaine-dependent probands/siblings

	Chi-Square	df	p-Value
Adolescent-onset cannabis use	11.4	1	0.0007 ^a
Proband/sibling effect	0.1	1	0.76
Proband-by-adolescent-onset effect	3.6	1	0.06

^aThe model was started with adolescent cannabis onset, COMT genotypes, and proband/sibling status and ended with significant main effect of adolescent cannabis onset, and marginally significant adolescent cannabis onset by proband/sibling interaction. Severity of cocaine dependence (i.e., DSM-IV symptom count) was controlled in the model.