

Novelty Seeking as a Phenotypic Marker of Adolescent Substance Use

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Supplementary Issue: Externalizing and Internalizing Symptomology and Risk for Substance Abuse: Unique and Interactive Influences

ABSTRACT: Trait novelty seeking has been consistently implicated in substance use, yet the origins and mechanisms of novelty seeking in substance use proneness are unclear. We aimed to characterize novelty seeking as a phenotypic marker of substance use proneness in adolescence, a critical period for drug use experimentation. To this end, we parsed novelty seeking's two constituent subdimensions – exploratory excitability (drive for novel experience) and impulsiveness (careless decision-making) – and explored the individual relations of these dimensions to: (1) the use of a variety of licit and illicit substances, (2) family history of substance use, and (3) subjective drug effects. Five hundred eighty five adolescents (mean age = 14.5 years) completed surveys of key variables. Results indicated that, when accounting for the covariation among exploratory excitability and impulsiveness, impulsiveness emerged as the more salient correlate of substance use and was independently associated with initiation of nearly all drug classes. Mediation analyses of the mechanisms of novelty seeking-related risk illustrated that impulsiveness mediated the association of family history of substance use with both initiation and past 30-day frequency of use. Both impulsiveness and exploratory excitability were associated with increased positive and negative subjective drug effects, and the analyses supported a significant indirect pathway from impulsiveness to a more frequent use via positive subjective effects. Although limited by a cross-sectional design, these findings suggest that impulsiveness-like aspects of the novelty seeking construct may represent a useful phenotypic marker for early substance use proneness that potentially (1) increases initiation risk, (2) has familial origins, and (3) promotes more frequent use by altering subjective drug response.

KEYWORDS: impulsivity, subjective effects, family history, drug reward, sensation seeking

SUPPLEMENT: Externalizing and Internalizing Symptomology and Risk for Substance Abuse: Unique and Interactive Influences

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Introduction

There is a consistent evidence that earlier onset of substance use is associated with increased risk for the subsequent development of a range of use-related problems and substance use disorders¹ with data indicating more severe adult outcomes in individuals who start using by age 14.^{2,3} Given the increased risk of poor outcomes for early initiators, characterizing phenotypic markers of adolescent substance use proneness may be useful for identifying those who ultimately

stand to benefit most from youth substance use prevention efforts. Furthermore, such information may elucidate etiological determinants of substance use risk and advance developmental psychopathology theory. We aimed to characterize trait novelty seeking as a phenotypic marker of substance use proneness in adolescence, a critical period for drug use experimentation.

A large body of literature supports a role for impulsive-like traits in substance use using a wide array of impulsivity



and related measures.^{4,5} Of the various constructs relevant to the impulsivity/risk-taking spectrum, the construct of novelty seeking⁶ may be a promising target for research on phenotypic markers of substance use proneness. Novelty seeking is a broad personality trait characterized by a tendency toward impulsive responding and exploratory behavior in search of novel and rewarding stimuli.^{6,7} Novelty seeking is genetically influenced by⁸ and associated with neural systems involved in behavioral activation and appetitive responses, including low basal dopaminergic activity.⁶ The psychobiological systems involved in novelty seeking (ie, reactivity to reward and dopaminergic neurotransmission) overlap with those of drug use disorders, indicating that novelty seeking is a theoretically plausible phenotypic marker for substance use proneness. Furthermore, novelty seeking reliably predicts later drug use disorder vulnerability,^{9,10} perhaps by increasing the variety and frequency of substances used. Although data clearly implicate novelty seeking in substance use, there are several gaps in the literature that require further attention in order to meaningfully characterize novelty seeking as a possible phenotype for early life substance use proneness.

One important limitation of prior work on novelty seeking is the lack of breadth in the types of substances assessed. While the literature has provided strong evidence in support of a relation between novelty seeking and adolescent tobacco and alcohol use,^{10–16} less is known regarding relations between novelty seeking and the use of other drugs during adolescence. Recent epidemiologic studies indicate that sizeable proportions of teens have experimented with various classes of drugs in recent years, particularly prescription drug misuse.^{17–20} Furthermore, given that recent changes in legislation have relaxed laws against marijuana use in some states in the US (eg, California, Washington, and Colorado), risk of marijuana use because of novelty seeking and other factors may be more likely to be expressed currently as opposed to several years ago. Hence, an up-to-date analysis of the relation between novelty seeking and the use of a variety of substances in an adolescent sample is warranted.

In addition, there have been a few studies that have isolated discrete subdimensions of novelty seeking. The novelty seeking construct as proposed by Cloninger et al can be parsed into excitability surrounding novel experiences (exploratory excitability, eg, “I often try new things just for fun, even if more people think it is a waste of time.”) and impulsive decision-making (impulsiveness, eg, “I often do things based on how I feel in the moment.”).²¹ Impulsiveness and exploratory excitability reflect unique dimensions of novelty seeking that may require different intervention approaches (eg, promoting fun and exciting healthy alternatives to substance use vs. enhancing mindful decision-making) depending on whether they have the same or different pathways to substance use proneness. Preliminary work suggests that these two constructs may differentially associate with particular drug use patterns and drug preferences in adults.²² Therefore, it is important to parse the

roles of exploratory excitability and impulsiveness in the work on initiation and early use of substances.

Further, more information is needed regarding the origins and mechanisms of risk pathways to comprehensively characterize novelty seeking as a putative phenotype for substance use proneness. Novelty seeking and substance use disorders tend to aggregate in families,²³ suggesting that the co-occurrence of novelty seeking and the risk for problematic substance use may reflect shared genetic etiologies and/or the possibility that the parenting styles and environments that substance using parents raise their children in may engender novelty seeking-related traits in offspring. Hence, the family history of substance use may be a starting point for novelty seeking-related risk of substance use, such that familial risk for substance use may exert influence on adolescent offspring substance use behavior via novelty seeking traits.

Finally, novelty seeking traits are associated with lower dopaminergic receptor availability in the human ventral mid-brain²⁴ and dopaminergic activation plays an important role in the subjective reinforcing effects of substances of abuse.^{25,26} Thus, the novelty seeking phenotype may represent an indication of a neurobiological profile that is more susceptible to substances of abuse. Along these lines, novelty seeking-related traits have been linked to a greater subjective response to a variety of substances of abuse in adults,^{27–33} which suggests that individuals high on impulsiveness or exploratory excitability may be susceptible to be more responsive to substances of abuse.^{9,10,34} Because greater sensitivity to subjective responses to substances has been associated with increased risk for heavier patterns of use and disorder across drugs (including tobacco, alcohol, and marijuana^{35,36}), variation in subjective responses as a function of impulsiveness may be a mechanism by which individuals are put on the risk pathway toward more frequent use and ultimately disorder. Examination of the pathway from novelty seeking to subjective drug effects to drug use frequency in adolescents could serve to clarify associations and help to establish evidence for mechanisms of risk early in the substance use disorder trajectory.

The current study characterized the novelty seeking dimensions of exploratory excitability and impulsiveness as phenotypic markers for substance use proneness in a cross-sectional survey of 14–16-year-old high school students. First, we examined the relation of exploratory excitability and impulsiveness to initiation across several classes of drugs, including tobacco, alcohol, marijuana, stimulants, opioids, barbiturates, sedatives, psychedelics, and prescription and over-the-counter drugs. Next, we used two types of mediation analyses to examine mechanistic pathways explaining the origins and intermediate processes underlying the relation between novelty seeking and use. Specifically, we examined the adolescent novelty seeking dimensions as mediators in the pathway linking adolescent report of their family history of substance use to their own substance use. We also tested the mediational hypothesis that novelty seeking traits are associated with



greater frequency of substance use via variation in subjective drug effects.

Method

Participants and procedures. All procedures were approved by the University of Southern California Institutional Review Board. Participants were ninth graders enrolled in one of the two participating public high schools in the Los Angeles metropolitan area and were invited to participate in a study on the relation between psychopathology and health behavior. All students were eligible to participate with the exception of those in either special education or English as a second language program. A total of 807 students were eligible. Of the 689 (85%) students who provided assent, 585 (82%) provided parental consent, were enrolled in the study, and were administered in the study survey. Students completed paper-and-pencil surveys assessing personality, psychopathology, and health behaviors administered on-site across two mandatory 40-minute class periods in May 2013. Data collectors explained that responses would be confidential and not shared with teachers, parents, or school staff, per a certificate of confidentiality from the federal government and the institutional review board. Descriptive statistics of demographic and substance use variables is presented in Table 1.

Measures. *Substance use.* Substance use measures from the Youth Risk Behavior Surveillance Survey (YRBSS) and the Monitoring the Future (MTF) questionnaire, which have been extensively validated in adolescents,^{17,18} were used to assess lifetime and past 30-day use frequency of a variety of illicit and licit prescription substances. Initiation (yes/no; any lifetime use) was coded for the following drug classes: any tobacco (ie, a whole cigarette, smokeless tobacco, or other forms of combustible tobacco), one full drink of alcohol, marijuana, any stimulant drug (ie, cocaine, methamphetamine, stimulant diet pills, or prescription stimulant without a doctor's advice), any opioid (ie, heroin, prescription opioid painkillers without a doctor's advice), any prescription drug without a doctor's advice (ie, prescription painkillers, stimulants, barbiturates, tranquilizers, or sedatives), any over-the-counter drug (ie, cough or cold medicines, diet pills, antihistamines), soft drugs (ie, a whole cigarette, alcohol, or marijuana), hard drugs (ie, inhalants, cocaine, meth, lysergic acid diethylamide (LSD), mushrooms, psychedelics, ecstasy, heroin, prescription painkillers, barbiturates, tranquilizers, or sedatives), or any substance (ie, all the above substances combined). Prevalence of use by class is reported in Table 2.

Frequency of use in the past 30 days (0 = no days, 1 = 1–2 days, 2 = 3–5 days, 3 = 6–9 days, 4 = 10–14 days, and 5 = 15–30 days) was assessed for only six substances (alcohol, tobacco, marijuana, illicit stimulants [eg, methamphetamine, cocaine], prescription stimulants [eg, adderall, ritalin], and prescription opioids [eg, oxyContin, vicodin]). Given the low variance in individual use for illicit substances and to reduce type I error rate, a composite frequency of use variable was created by summing the frequencies reported across all six substances.

Table 1. Sample demographic, personality, and substance use variables ($N = 585$).

Gender		
Female	285	48.7%
Male	297	50.8%
Missing	3	0.5%
Age, N (%)		
14	304	52%
15	268	45.8%
16	11	1.9%
Missing	2	0.3%
At least one parent completed high school	454	77.6%
Ethnicity		
American indian or Alaska native	4	0.7%
Asian	33	5.6%
Black or African American	12	2.1%
Hispanic or Latino	285	48.7%
Native Hawaiian or Pacific Islander	14	2.4%
White	132	22.6%
Other	63	10.8%
I cannot choose only one term	26	4.4%
Missing	16	2.7%
Substance use, past 30 days full sample (males)		
Alcohol	103 (38)	17.6% (6.5%)
Tobacco	21 (7)	3.6% (1.2%)
Marijuana	75 (36)	12.8% (6.2%)
Illicit stimulants	4(3)	0.7% (0.5%)
Prescription stimulants	16 (7)	2.7% (1.2%)
Prescription opioids	33 (11)	5.6% (1.9%)
Personality		
TCI impulsiveness (range 0–5), M (SD)	2.0	(1.1)
TCI exploratory excitability (range 0–4), M (SD)	2.3	(1.5)
Family history		
Alcohol problems	185	31.6%
Cigarette smoking	393	67.2%
Drug problems	120	20.8%
Total positive subjective effects across substances (range 0–6), M (SD)	5.6	(4.4)
Total negative subjective effects across substances (range 0–6), M (SD)	3.2	(3.5)

Notes: Subjective effects subscales reflect summary scores of the total positive and negative subjective effects reported for all substances used in the past six months. Total may not add up to 100% because of occasional missing data.

Abbreviation: TCI, Temperament and Character Inventory.

Novelty seeking. Two novelty seeking subscales, impulsivity (five true/false items, eg, “I often do things based on how I feel at the moment,” “I like to make quick decisions so I can get on with what has to be done”) and exploratory excitability

**Table 2.** Single and combined logistic regressions with measures of novelty seeking predicting initiation of substances.

SUBSTANCE	% YES	SINGLE				COMBINED			
		TCI EXPLORATORY EXCITABILITY		TCI IMPULSIVENESS		TCI EXPLORATORY EXCITABILITY		TCI IMPULSIVENESS	
		β	OR	β	OR	β	OR	β	OR
Any tobacco	21	0.39****	1.48	0.48****	1.62	0.27*	1.31	0.40***	1.49
One full drink	41	0.36****	1.43	0.42****	1.51	0.25**	1.29	0.34***	1.40
Marijuana	25	0.33***	1.39	0.50****	1.64	0.19	1.21	0.44****	1.54
Stimulants	5	0.26	1.29	0.54*	1.46	0.15	1.16	0.33	1.39
Opioids	6	0.55**	1.74	0.74****	2.10	0.36	1.43	0.64**	1.89
Prescription	6	0.18	1.20	0.30	1.34	0.09	1.09	0.27	1.31
Over the counter	6	0.05	1.05	0.34*	1.41	-0.07	0.93	0.37*	1.44
Soft drugs	46	0.36****	1.43	0.41****	1.50	0.25*	1.29	0.33***	1.38
Hard drugs	15	0.45***	1.57	0.73****	2.08	0.25	1.28	0.66****	1.94
Any substance	50	0.35****	1.41	0.43****	1.53	0.23**	1.26	0.35****	1.42

Notes: Ns range from 579 to 580. Estimates are standardized. Single models include either exploratory excitability or impulsiveness as the sole predictor, and combined models include exploratory excitability and impulsiveness as simultaneous predictors. Covariates in all models included age, gender, ethnicity, and years of parental education. Any tobacco: a whole cigarette, other forms of tobacco, and smokeless tobacco; stimulants: cocaine, meth, diet pills, and Rx stimulants; opioids: heroin and Rx painkillers; prescriptions: Rx painkillers, barbiturates, tranquilizers or sedatives, and Rx stimulants; over the counter: cough or cold medicines, diet pills, and antihistamines; soft drugs: a whole cigarette, alcohol, and marijuana; hard drugs: inhalants, cocaine, meth, LSD, mushrooms, psychedelics, ecstasy, heroin, Rx painkillers, barbiturates, and tranquilizers or sedatives; and any substance: all listed drugs. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

(four true/false items, eg, “I often try new things just for fun and thrills,” “When nothing new is happening, I usually start looking for something that is thrilling or exciting”), of the abbreviated 55-item Temperament and Character Inventory (TCI) were administered.²¹ Total scores are created by summing individual item scores for nonreversed (T = 1, F = 0) and reversed scored (T = 0, F = 1) items; possible range for impulsiveness was 0–5 and exploratory excitability 0–4. Variants of TCI novelty seeking scales have been used successfully in prior research in adolescents and have demonstrated adequate psychometric properties.³⁷

Family history. Family history was assessed with three questions: Does anyone in your immediate family (brothers, sisters, parents, and grandparents) have a history of (1) smoking cigarettes (yes/no), (2) alcohol abuse problems (yes/no), and (3) drug abuse problems (yes/no). Responses on these items were summed to create an index of family history of substance use (yes = 1, no = 0; summed score range of 0–3). This approach is supported by prior work showing that familial loading confers broad risk for substance use primarily through a general vulnerability to problematic use across substances.^{38,39}

Acute subjective drug effects. Acute subjective drug effects were measured using a variant of the 12-item modified Lyons battery for subjective effects (M-LBSE).^{35,40,41} For each of the six substances (alcohol, tobacco, marijuana, illicit stimulants, prescription stimulants, and prescription opioids), participants were asked, “Over the past 6 months, in the period shortly after you [used substance] did it make you feel [subjective effect]” (yes/no/never used). Participants who had not used a particular substance in the past six months did not complete the M-LBSE items for that substance. The

M-LBSE includes two subscales assessing rewarding (eg, euphoric, relaxed, energetic) and aversive (eg, drowsy, unable to concentrate, lazy) experiences that were used to create two composite scores – a cross-substance positive and a negative subjective effects score for each individual. Each score was the sum of the respective rewarding and aversive effects of all drugs reported for a given individual. We used this approach, first, because there was low frequency of use for some substances, leaving little M-LBSE data for certain substances and, second, because prior population-based research using the M-LBSE has found strong cross-substance associations within drug-specific positive effect scales and within drug-specific negative effect scales, as well as evidence of cross-substance associations between drug effects of one substance and use of another.⁴²

Statistical analyses. All analyses were executed in SPSS 19.0.⁴³ Gender, age, ethnicity, and years of parental education were included as covariates in all the models. Significance was set to 0.05 (two-tailed) for each analysis.

Logistic regressions were used to examine TCI exploratory excitability and impulsiveness as predictors of initiation (yes/no; any lifetime use) of various substances. We sought to examine the variance accounted for by the subscales individually as well as the unique predictive power of each subscale over and above the other. Thus, for each outcome (single substance or class of substances), three types of models were calculated: (1) a univariate model that included impulsiveness as the sole predictor, (2) a univariate model that included exploratory excitability as the sole predictor, and (3) a combined model that included impulsiveness and exploratory excitability as simultaneous predictors to examine their unique associations

with outcomes after controlling for their covariance. We followed up these main effects with selected mediation in order to examine the mechanisms underlying the novelty seeking and substance use relationship. These analyses used the any substance class in order to reduce the number of tests performed and type I error risk and because of prior evidence of cross-substance relations (eg, Ref. 42).

Mediation was tested via the products of the coefficients method, which provides an estimate of the a (independent variable [IV]–mediator [M]), b (M–independent variable [DV]), c (total effect of IV on DV), and ab (indirect effect of IV on DV via M) paths for each mediation model.⁴⁴ Because the assumption of normality of the sampling distribution of total indirect effects is questionable, bias-corrected 95% confidence intervals (CIs) of the indirect effect were also estimated using bootstrapping methods.⁴⁴ First, we tested the novelty seeking subscales as mediators of the association of family history of substance use and initiation and frequency of substance use. This association was tested using multiple mediation with family history of substance use score as the IV, impulsiveness and exploratory excitability as simultaneous Ms, and yes/no initiation of the use of any substance as the DV. We ran parallel mediation analyses of family history via impulsiveness/exploratory excitability that substituted past 30-day frequency of any substance use as the DV. Next, we examined whether novelty seeking exerts its influence on use through an indirect effect of acute subjective drug effects. In these models, either impulsiveness or exploratory excitability was the IV, cross-substance positive and negative subjective effect composite scores were simultaneous Ms, and past 30-day use frequency for the any substance class was the DV. In addition to the covariates listed above, family history of substance use was included as a covariate in these models in order to examine whether any significant associations among novelty seeking, acute subjective effects, and frequency of use were present over and above an effect of family history. Significant mediation pathways were followed up with exploratory tests of reverse mediation in which the M and DV are reversed in the model. If mediation is not supported in these reverse models, it provides additional support for the directionality of the proposed mediation pathway in cross-sectional data (eg, Ref. 45). Results of regression models are reported as odds ratios (ORs) with 95% CIs for binary outcomes and betas (β s) for continuous outcomes, and parameter estimates are unstandardized.

Results

Correlations between novelty seeking subscales.

Exploratory excitability and impulsiveness subscales were correlated at $r = 0.34$, $P < 0.001$, which indicates that the two indexes assess related but separable constructs.

Relations of novelty seeking to substance use initiation. The results for the individual and combined models testing the relations of novelty seeking dimensions on initiation of

various types and classes of substances are reported in Table 2. In the individual models, associations with impulsiveness were significant for nearly all outcomes; the association with prescription drugs was trend level. Significant associations with exploratory excitability were also found for nearly all outcomes examined; exceptions were stimulants, prescriptions, and other over-the-counter drugs. In the combined models, impulsiveness was independently associated, again, with nearly all outcomes; the independent effect of exploratory excitability over and above impulsiveness was evident for tobacco, alcohol, soft drugs (tobacco, alcohol, and marijuana combined), and any substance (all drug classes combined).*

Mediational analyses. Table 3 reports the model results for the a (IV–M), b (M–DV), c (total effect of IV on DV), and ab (indirect effect of IV on DV via M) paths for all mediation analyses. The results are described below.

Novelty seeking subdimensions as mediators of the association of family history with lifetime initiation and past 30-day frequency of substance use. Family history score (IV) was associated with higher levels of impulsiveness (M; a_1 path; $\beta = 0.04$, SE = 0.01, $P < 0.001$), and impulsiveness (M) was associated with increased frequency of substance use likelihood of substance initiation for any substance (DV; b_1 path; $\beta = 1.01$, SE = 0.33, $P < 0.01$). In addition, the indirect effect of family history score (IV) on any substance initiation (DV) through impulsiveness (M) was significant (ab_1 path: $\beta = 0.04$ [95% bias-corrected CI = 0.01–0.09], SE = 0.02, $Z = 2.43$, $P < 0.01$). Importantly, this indirect effect through impulsiveness was significant over and above exploratory excitability and demographic covariates. In contrast, although there was a significant association between exploratory excitability (M) and substance initiation (DV; b_2 path; $\beta = 0.80$, SE = 0.37, $P = 0.03$), there was no significant association between family history (IV) and exploratory excitability (M; a_2 path; $\beta = 0.01$, SE = 0.01, $P = 0.30$). Additionally, the indirect effect of family history (IV) on substance initiation (DV) through exploratory excitability (M) was not significant (ab_2 path; $\beta = 0.01$ [95% bias corrected CI = –0.01–0.05], SE = 0.01, $Z = 0.86$, $P = 0.39$). The pattern of results was the same in models testing past 30-day frequency of use as the IV. The results of these models are displayed in Figure 1.

Subjective effects as a mediator of the relationship of novelty seeking subscales and frequency of substance use. In these models of the subsample of individuals who reported using at least one of the six substances in the past six months and reported on subjective effects of those substances over that time frame ($n = 230$), impulsiveness (IV) was associated with higher levels of positive (M; a_1 path; $\beta = 2.11$, SE = 0.99, $P < 0.05$) and negative (M; a_2 path; $\beta = 2.20$, SE = 0.82, $P < 0.01$) cross-substance subjective effects composites; further, positive

*Post hoc analyses testing the nine individual novelty seeking items in a combined model predicting substance use initiation across drug classes suggested evidence of unique predictive value for several individual impulsiveness items and one exploratory excitability item (detailed results available upon request to the first author).

Table 3. Results of mediation analyses testing novelty seeking as a mechanism in the pathway of risk for substance initiation and use.

IV–M – DV	N	A PATH		B PATH		C PATH		AB PATH (INDIRECT EFFECT)			
		β	T	β	T	β	T	β	Z	95% CI	
Family history score–novelty seeking – initiation (yes/no) of any substance											
Overall model	556	Model $X^2 = 78.1$, $R^2 = 0.14$, $P < 0.00001$									
Impulsiveness		0.04**	2.84	1.01**	3.10	0.80*	2.16	0.04*	2.43	0.01	0.09
Exp. excitability		0.01	1.03	0.80*	2.16	0.80*	2.16	0.01	0.91	–0.01	0.05
Family history score–novelty seeking–frequency of use of any substance											
Overall model	556	$F = 5.4$, Adj $R^2 = 0.06$, $P < 0.00001$									
Impulsiveness		0.04**	2.84	1.28**	3.12	0.29*	2.31	0.06**	2.46	0.01	0.12
Exp. excitability		0.01	1.03	0.76	1.65	0.29*	2.31	0.01	0.86	–0.01	0.05
*Novelty seeking–positive and negative subjective effects†–frequency of use of any substance											
Impulsiveness–overall model	230	$F = 20.6$, Adj $R^2 = 0.41$, $P < 0.00001$									
Positive subjective effects		2.11*	2.02	0.44****	7.20	0.44****	7.20	0.93*	2.05	0.02	1.95
Negative subjective effects		2.20**	2.68	0.20**	2.53	0.44****	7.20	0.43	1.83	0.05	1.21
Exp. excitability–overall model	230	$F = 20.6$, Adj $R^2 = 0.41$, $P < 0.00001$									
Positive subjective effects		2.33	1.89	0.44****	7.17	1.36	1.27	1.03	1.82	–0.06	2.26
Negative subjective effects		1.32	1.34	0.20**	2.53	1.36	1.27	0.26	1.18	–0.07	0.99

Notes: a path = independent variable (IV)–mediator (M), b path = mediator (M)–dependent variable (DV), c path = total effect of IV on DV, and ab path = indirect effect of IV on DV via M. 95% CI are bootstrapped bias corrected estimates of indirect effects. Covariates for all models included age, gender, ethnicity, and years of parental education. *Family history score was included as an additional covariate in these models. *Mediators were two separate subscales summing the positive and negative subjective effects reported for all substances used in the past six months. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

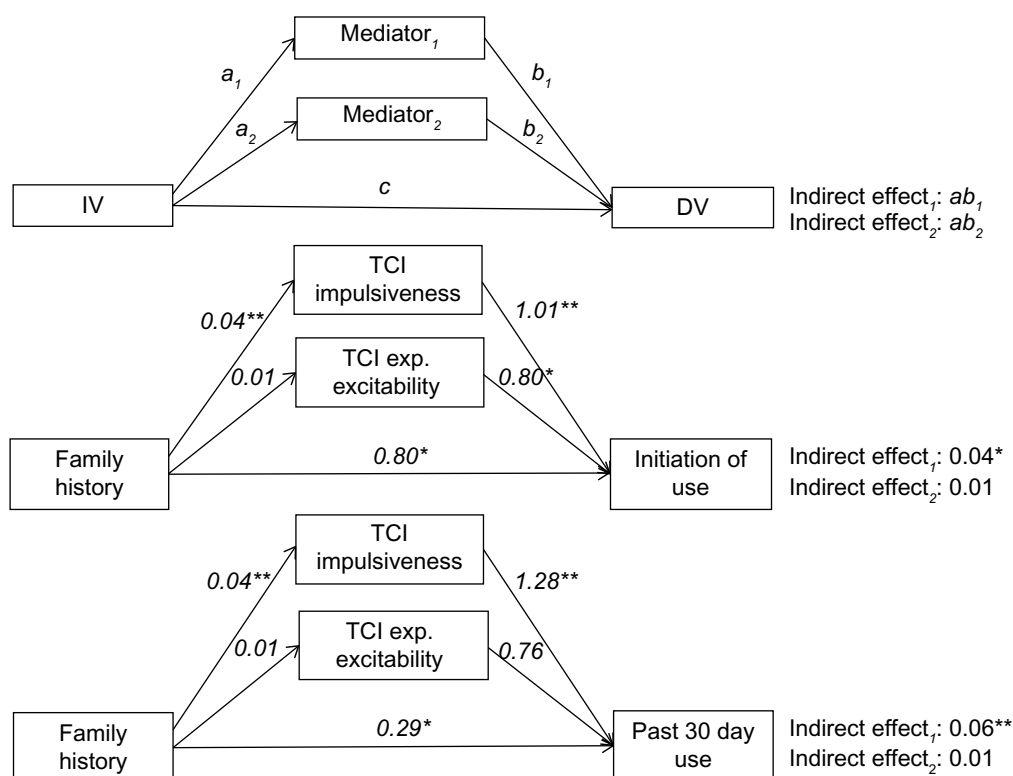


Figure 1. Mediation models testing TCI novelty seeking dimensions, impulsiveness, and exploratory excitability in the relationships among family history of substance use and early adolescent substance use ($n = 556$). Mediation was tested via the products of the coefficients method⁴⁴ with family history of substance use score as the IV, impulsiveness (M_1) and exploratory excitability (M_2) as simultaneous mediators, and yes/no initiation of use of any substance as the dependent variable (DV). A parallel model was run substituting past 30-day frequency of any substance use as the DV ($n = 556$). Gender, age, ethnicity, and years of parental education were included as covariates in both the models. The results indicate a significant indirect effect from the family history of substance use to both substance initiation and past 30-day use frequency through impulsiveness. Significant mediation through impulsiveness was present over and above exploratory excitability and important demographic covariates.

(M; b_1 path; $\beta = 0.44$, $SE = 0.06$, $P < 0.0001$) and negative (M; b_2 path; $\beta = 0.20$, $SE = 0.08$, $P < 0.01$) subjective effects were both associated with more frequent use of substances (DV). In addition, the indirect effect of impulsiveness on frequency of use through positive subjective effects was significant (ab_1 path: $\beta = 0.93$ [95% bias corrected CI = 0.02–1.95], $SE = 0.48$, $Z = 2.05$, $P < 0.05$), see Figure 2. Although exploratory excitability and positive subjective effects were associated at trend level (a_1 path; $\beta = 2.33$, $SE = 1.89$, $P < 0.10$), there was no significant indirect effect through positive (ab_1 path) or negative (ab_2 path) subjective effects (ab_1 paths) for the models with exploratory excitability as the independent variable. All significant effects were present over and above family history score and demographic covariates.

Post hoc tests of reverse mediation. For the models supporting impulsiveness as a mediator of the family history \rightarrow substance use relationship, the alternative reverse mediation model was tested with family history as the IV, substance use as the M, and impulsiveness as the DV, controlling for all original covariates and exploratory excitability. Reverse mediation was supported for both lifetime initiation (ab path; $\beta = 0.01$ [95% bias-corrected CI = 0.005–0.02]) and past 30-day frequency of use (ab path; $\beta = 0.003$ [95% bias-corrected CI = 0.0003–0.01]). For the models supporting subjective effects as a mediator of novelty seeking and substance use frequency, the reverse mediation model was tested with impulsiveness as the IV, past 30-day frequency of use as the M, and positive subjective

effects as the DV, controlling for all original covariates and negative subjective effects as an additional covariate. In this model, reverse mediation was not supported (ab path; $\beta = 0.16$ [95% bias-corrected CI = –0.85–1.03]).

Discussion

In this study of the role of novelty seeking dimensions in substance use in 14–16-year olds, we found relatively clear evidence suggesting that impulsiveness reflects a phenotypic marker of substance use proneness. While both impulsiveness and exploratory excitability were individual predictors of substance initiation across most drug classes, impulsiveness emerged as a consistent independent predictor of initiation across nearly all classes of licit and illicit substances when accounting for the covariation among these two dimensions of novelty seeking. Similarly, only impulsiveness was associated with a family history of substance use. Further, impulsiveness, but not exploratory excitability, mediated the association of family history with both initiation and past 30-day use frequency. However, post hoc reverse mediation models indicate that our data do not allow us to rule out the possibility that substance use leads to impulsiveness based on the cross-sectional design. Finally, a significant indirect effect from impulsiveness to more frequent substance use via positive (but not negative) subjective drug effects was found, and results from reverse mediation models suggested that an alternative direction of this pathway was unlikely. Exploratory excitability did not display indirect

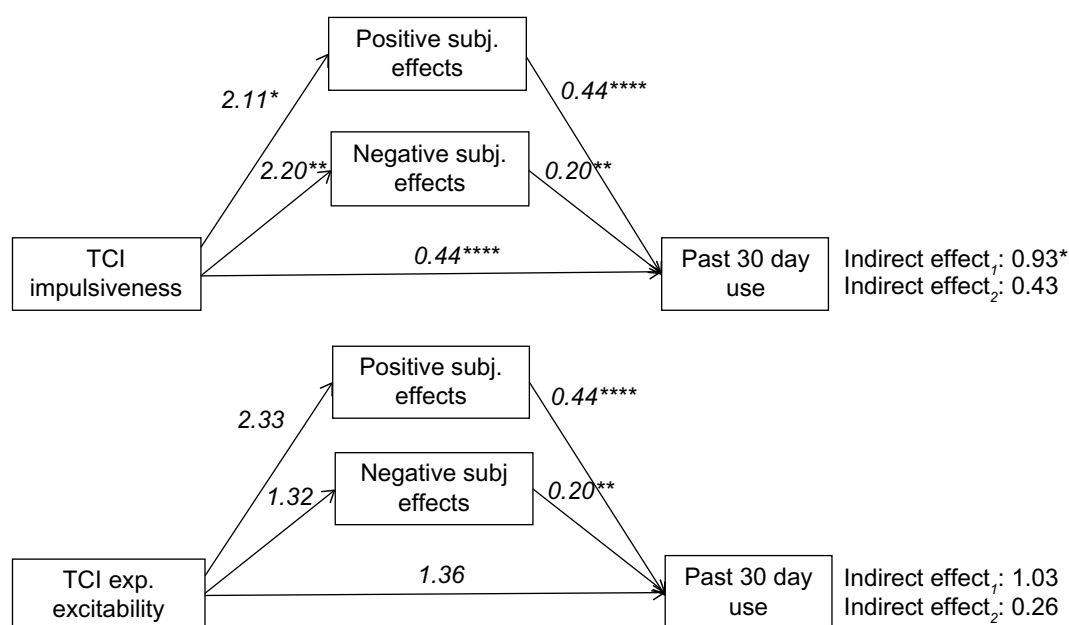


Figure 2. Mediation models testing cross-substance positive and negative subjective effect composite scores in the relationship among TCI impulsiveness and past 30-day use frequency of any substance ($n = 230$). Mediation was tested via the products of the coefficients method⁴⁴ with TCI impulsiveness as the IV, positive (M_1) and negative (M_2) as cross-substance, subjective effects, simultaneous mediators, and past 30-day frequency of any substance as the DV. A parallel model was run substituting TCI exploratory excitability as the IV ($n = 230$). Family history of substance use, gender, age, ethnicity, and years of parental education were included as covariates in both the models. The results indicate a significant indirect path from impulsiveness to frequency of use of any substance over the past 30 days through positive subjective drug effects. Significant mediation through positive subjective effects was present over and above negative subjective effects and important demographic covariates.



effects on substance use frequency via subjective effects. Thus, although exploratory excitability traits were associated with initiation into substance use via alcohol and tobacco, impulsiveness played a more salient role in vulnerability to substance use more generally and in mechanistic pathways related to family history and subjective drug effects.

These findings are consistent with the larger literature suggesting a role for impulsivity- and excitement seeking-related traits in substance use risk.⁴ Further, given the above-mentioned findings, these data suggest that the impulsiveness facet of the broad spectrum of characteristics associated with novelty seeking may be particularly important for adolescent substance use proneness. These results are consistent with prior work indicating that individuals with drug use disorders and a family history of such disorders present with impulsivity-related cognitive and neuropsychological deficits (eg, poor inhibitory and executive control⁴⁶). To the extent to which the current family history results reflect genetic factors, our findings may also cohere with evidence illustrating that the effects of dopaminergic gene variants on adolescent and young adult substance use are mediated by novelty seeking.^{47–49} Hence, there is converging evidence that impulsiveness and associated deficits in inhibitory control may represent a phenotypic manifestation reflecting vulnerability to adolescent substance use. Although our cross-sectional data cannot differentiate a causal role of impulsivity on substance use, our findings and others' findings clearly support a genetic and environmental risk pathway implicating a combined role of family history and impulsivity with increased substance initiation and use.

With regard to subjective responses, our data extend links among novelty seeking-like traits and acute subjective effects of substances that have mostly been found in adults in an adolescent sample.^{27–33} Higher impulsiveness and exploratory excitability were both associated with greater positive and negative subjective responses, suggesting that high novelty seeking individuals are more likely to report stronger overall effects from early drug experiences. This is consistent with prior evidence in adults pointing to associations among novelty seeking personality factors and stronger subjective sense of stimulation from D-amphetamine.³³ In addition, our data support a sensitivity model, such that high-intensity subjective reactions are predictive of later use regardless of whether these experiences were positive or negative, and is consistent with some prior works.^{50–53} By contrast, other studies have reported that only positive reactions to a drug are predictive of later regular use and that negative reactions may protect against future use.^{41,54–56} Given that the indirect path from impulsiveness to frequency of use was present for only positive subjective effects and nonsignificant reverse mediation was consistent with this directional pathway, our findings point toward rewarding effects as potentially channeling risk from experimentation to more frequent use in highly impulsive teens.

Conclusions

The conclusions that can be drawn from our results should be interpreted in the context of several important limitations. Relationships assessed in our study are limited by the cross-sectional nature of our data, and we therefore cannot ascertain directionality or causality. We also rely exclusively on retrospectively reported acute drug effects over the prior six months. While consistent with the approach taken by most naturalistic studies examining subjective drug effects,^{52,53,57} an important possible confound is that individuals who use more frequently also use at higher doses and therefore simply report stronger pharmacologically mediated effects because of elevated drug levels, though reverse mediation results suggested that the relation of impulsiveness to substance use frequency was more likely mediated by (and not resulting in) enhanced positive subjective effects. We did not collect data on drug dose or use intensity and therefore cannot address this issue or speak to drug use intensity patterns (eg, binge use). Hence, convergence of these data with longitudinal designs, laboratory drug administration designs, and reports of effects more proximal to the use experience would be beneficial. Also, given the low prevalence of initiation and use of stimulant, prescription, and over-the-counter drugs, analyses may have been underpowered to detect associations with novelty seeking for these specific drug types. In addition, while we statistically adjusted for important demographics, there are many other variables to be considered as possible covariates (eg, peer use, availability/access to substances, mental health). These factors may be involved in novelty seeking risk pathways (eg, impulsive teens may intentionally seek out deviant peers who use substances), and future work should seek to determine the extent to which these associations are shared by exploratory excitability and impulsiveness dimensions as well as the role of these factors in novelty seeking–substance associations. The novelty seeking scales used in the current study were brief and might have been prone to measurement error, although both impulsiveness and exploratory excitability exhibited criterion validity in that they were meaningfully associated with substance use and each other. Finally, the family substance use scale did not ask about the level of use or frequency, but rather endorsement of problematic use or not.

Limitations notwithstanding, this study provides one of the most comprehensive examinations of novelty seeking as a possible phenotypic marker of adolescent substance use proneness to date. Taken together, the current findings may reflect a risk pathway whereby family history of substance use promotes impulsiveness in offspring, a trait that may heighten risk of early experimentation with a variety of drug classes. Teens with high impulsiveness may be more sensitive to the subjective effects of drugs, and the rewarding aspects of the drug use experience may ultimately reinforce future drug-taking behavior and substance use escalation. Such findings,

if supported by longitudinal investigations, may lead to more targeted primary prevention and intervention strategies for teens at risk for early or problematic use because of their personality or family profiles.

IRB Approval, Informed Consent, and Declaration of Helsinki Compliance

This study conforms to recognized ethical standards for the treatment of human subjects and was approved by the University of Southern California Institutional Review Board and with the Helsinki Declaration of 1975, as revised in 1983. Both parental consent and adolescent assent were obtained prior to study participation.

Author Contributions

Conceived and designed the experiments: LCB, AML, JAM. Analyzed the data: LCB. Wrote the first draft of the manuscript: LCB. Contributed to the writing of the manuscript: TRG, LCB, AML. Agree with manuscript results and conclusions: LCM, VSK, JAM, TRG, NSS, LAR, NRR, CRG, RDP, AML. Jointly developed the structure and arguments for the paper: LCM, VSK, JAM, TRG, NSS, LAR, NRR, CRG, RDP, AML. Made critical revisions and approved final version: LCM, VSK, JAM, TRG, NSS, LAR, NRR, CRG, RDP, AML. All authors reviewed and approved of the final manuscript.

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