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Longitudinal Modeling of the Association Between Transmissible Risk, Affect During Drug Use and Development of Substance Use Disorder

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Abstract

Objective—This longitudinal investigation examined the hypothesis that subjective experience during consumption of preferred drugs mediates the association of transmissible risk for substance use disorder (SUD) measured in childhood and adolescence and SUD diagnosis in adulthood. Transmissible risk denotes the psychological characteristics having intergenerational continuity between parents and their biological children.

Methods—The *transmissible liability index* (TLI) was administered to 483 10–12 year old boys (baseline). Follow-up evaluations were conducted when the boys attained 12–14, 16, 19 and 22 years of age using age-specific versions of the TLI. Frequency of consumption of the participant's three most preferred drugs, affect on an ordinary day, affect while under influence of the preferred substances and presence/absence of current SUD were assessed at 22 years of age.

Results—Consumption frequency of preferred drugs among boys mediates the association of transmissible risk during childhood and adolescence and SUD diagnosis in adulthood. Severity of negative affect on a drug-free day predicts frequency of consumption of preferred drugs which, in turn, predicts severity of negative affect during the drug use event. Neither affect on a drug-free day nor affect during the drug use event mediates the association of transmissible risk and SUD.

Conclusions—Affect on drug-free days, and while under influence of preferred substances covary with consumption frequency; however, affect is not related to transmissible SUD risk or SUD outcome.

Keywords

heritable risk; emotion; children; prospective research; etiology; addiction

Children of parents with substance use disorder (SUD) are at heightened risk to develop SUD. The characteristics during childhood associated with SUD risk include poor

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modulation of emotions, behavior under control, attention and executive cognitive deficits and irregular eating and sleeping routines (Tarter et al., 2012a). These varied manifestations of psychological dysregulation are indicators of transmissible (intergenerational) risk for SUD, reflecting combined heritable and parental rearing influences. Moreover, the characteristics comprise a continuous trait termed the *transmissible liability index (TLI)*. Notably, heritability accounts for 71%–85% of score variance (Vanyukov et al., 2009; Hicks et al., 2012; Vanyukov et al., 2015), and consistent with shared genetic and phenotypic liability (Tsuang et al., 1998; Kendler et al., 2003a; Kendler et al., 2003b), the TLI score predicts all substance use disorder (SUD) categories (Ridenour et al., 2011).

Prospective investigations have shown that the TLI in 10–12 year old boys predicts age of first substance use presaging SUD, negatively covaries with duration between first substance use and SUD, and forecasts SUD diagnosis during adolescence and adulthood (Kirisci et al., 2013a). Significantly, the TLI is a better predictor of SUD than externalizing behavior (Kirisci et al., 2015) and family history of SUD (Ridenour et al., 2011). Furthermore, childhood TLI predicts SUD severity in adulthood (Kirisci et al., 2015). Although other intrafamilial (e.g. siblings) and extrafamilial (e.g. peers, neighborhoods) factors additionally contribute to risk, rate of development and severity of SUD, the findings to date illustrate that the TLI is a practical tool for identifying individuals requiring intervention (Tarter et al., 2012).

Little is known, however, about the factors that bias high risk youths toward SUD outcome. A recent study observed that boys having high transmissible risk exhibit a linear *increase* in risk throughout adolescence after initial consumption that culminates in cannabis use disorder by early adulthood whereas low scoring children exhibit a progressive *decline* in risk (Kirisci et al., 2013b). These findings are intriguing insofar as heritability partly accounts for quality of drug-induced subjective experience (Grant et al., 2005) as well as risk for developing drug dependence (Lyons et al., 1997). Accordingly, it is theorized in this study that drug reward experience mediates the association between transmissible risk and substance use leading to SUD.

Confirming that subjective experience during the drug use event mediates the association between transmissible risk and substance use leading to SUD outcome has important ramifications for prevention. Specifically, the importance of impeding onset of substance use, even for legal substances, is underscored. For example, youths who frequently consume hyper caffeinated beverages (i.e. “energy drinks”) exhibit psychological characteristics that map closely to the TLI and are at high risk to develop SUD consequent to alcohol and drug use (Arria et al., 2011). Because concentrated caffeine is readily available in beverages (as well as powder form legally purchased on the internet), the affective experience in high risk youths may potentiate habitual consumption as well as progression to more potent or dangerous substances. Hence, showing that drug-induced affect mediates the association of transmissible risk and substance use segueing to SUD underscores the need to avert consumption onset in vulnerable youths and devise treatment interventions for substance misuse targeted at reducing motivation to obtain the desired affective experience.

Methods

Participants

Boys were recruited through their biological fathers who qualified for DSM-III-R lifetime diagnosis of SUD consequent to consumption of an illegal drug ($N = 235$) or had no adult psychiatric disorder ($N = 248$). Following baseline evaluation at age 10–12 they were re-evaluated at 12–14, 16, 19 and 22 years of age. Good health determined by medical history and physical examination and a full scale WISC-III IQ of at least 80 were required for inclusion in this study. Portions of this longitudinally tracked cohort have been studied previously (see www.pitt.edu/~cedar/publications.html) for list of publications); however, the present investigation does not overlap with or replicate prior research. Recognizing that there are numerous gender difference in SUD etiology, it is important, therefore, to conduct sex specific investigations. Accordingly, this study was confined to boys because development of the predictor measure, the transmissible liability index (TLI), is still undergoing validation studies in females.

Attrition between baseline (age 10–12) and outcome (age 22) was 38%. This high attrition rate is not unexpected considering that parents had SUD related to use of illegal drugs, thereby resulting in frequent moving to new locations. Failure to locate the participant (27.1%) was the most frequent reason for attrition despite an intensive tracking procedure and use of a national company specializing in locating “missing” individuals. Other factors impeding follow-up were incarceration and overseas military deployment. Only 14.1% of attrited subjects expressed lack of interest. Comparison of baseline data in retained and attrited participants, shown in Table 1, indicates that grade in school and ethnicity were not different. IQ was approximately six points lower in subjects who subsequently attrited ($F = 20.79$, $p < .001$); however, both segments of the sample scored in the normal range of intelligence. Family socioeconomic status (SES) measured by the Hollingshead index was on average two points lower in boys who attrited ($F = 5.41$, $p = .02$). Importantly, the transmissible liability index (TLI), the predictor variable, was not different between retained and attrited participants. In addition, the multivariate test of equivalence, shown in the right column of Table 1, reveals that retained and attrited participants are not systematically different, albeit the attrited segment of the sample was somewhat more psychosocially disadvantaged at the time of recruitment.

Instrumentation

Transmissible risk—The theory underlying development of the *Transmissible Liability Index (TLI)* (Vanyukov et al., 2003b), the methodology used to derive this index (Vanyukov et al., 2003a), and its psychometric properties (Kirisci et al., 2009; Vanyukov et al., 2009) have been described in detail. At the outset, faculty at the Center for Education and Drug Abuse Research (CEDAR) catalogued the psychological traits that have been implicated to be associated with risk for SUD. Next, items from CEDAR’s database were assigned to each trait. Exploratory factor analysis (EFA) followed by confirmatory factor analysis (CFA) verified unidimensionality of each construct. Items having loading $< .4$ and constructs that did not satisfy criteria for unidimensionality were deleted from further consideration. Comparisons of sons of fathers having a DSM-III-R diagnosis of a SUD related to an illicit

drug (SUD+) and psychiatrically normal fathers (SUD-) on each construct were conducted. The items contained in the constructs that discriminated the two groups of children of SUD were submitted to EFA and CFA to yield a final continuous trait. Lastly, item response theory (IRT) methodology was applied to calibrate the items. Five validated age-specific versions of the TLI (Kirisici et al., 2012) having IRT-derived reliability of .93, .91, .95, .93, and .93 were administered to the participants when they were 10–12, 12–14, 16, 19 and 22 years of age. The raw score at each time point was normalized to a z-distribution ($M = 0$, $SD = 1$) and equated using common items which enable comparison of scores across assessments on a common scale. The set of items, encompassing diverse indicators of self-regulation related to emotions, behavior and daily rhythms (e.g. eating, sleeping), can be found at www.pitt.edu/~cedar/tlidocument.html

Consumption of preferred substances (age 22)—Frequency of consumption was recorded using the self-report Substance Use Questionnaire (SUQ) (CEDAR, unpublished). The most frequently endorsed preferred substances were alcohol ($N = 40.9\%$) and cannabis ($N = 31.8\%$). The number of days in the past year ($N = 53.3$ days, $SD = 82.92$) a preferred substance was consumed was computed by prorating the number of consumption events in the past week or month.

Affect (age 22)—Affect was rated on five 100 mm visual analog scales presented one at a time on a touch screen for each of the participant's three most preferred substances. The participants responded to the question “*For each set of words listed below, select a point on the line which best describes how you feel on an ordinary day?*” The low-high anchors on the scales were: *excited-calm*, *unhappy-happy*, *upset-peaceful*, *tense-relaxed*, and *uncomfortable-comfortable*. Thus, a high mark toward the right side reflects stronger positive affect whereas a mark below the midpoint reflects stronger negative affect. The mean score for the sample on a drug-free day was averaged across the five scales was 34.6 ($SD = 23.3$), thereby indicating an overall baseline state of negative affect (neutral score = 50).

Next, the scales were presented again three times to record affect during the consumption event pertaining to the 1st, 2nd and 3rd most preferred drugs. Responses were recorded on the touch screen to the question: “*When you use this drug, how does it make you feel? Select a point on the line which best describes HOW YOU FEEL AFTER YOU HAVE TAKEN IT.*” The mean score was 35.4 ($SD = 22.42$), indicating the presence of negative affect while under the influence of their preferred substances. Notably, self-reported affect is almost identical while drug-free or in a drug-induced state.

Substance Use Disorder (age 22)—The outcome variable was current DSM-IV SUD diagnosis (abuse or dependence) consequent to consumption of any compound other than tobacco. A clinical committee consisting of two psychiatrists and the clinical associates who administered the interviews collectively formulated diagnoses based on the results of the SCID (Spitzer et al., 1990). The most frequent SUDs pertained to alcohol (27.6%) and cannabis (26.2%) consistent with the pattern of endorsement of preferred drugs.

Procedure

Written informed consent was obtained from parents when their sons were 10–12, 12–14 and 16 years of age. The boys also read and signed an assent form. In addition, the boys were queried to ensure that they were not coerced by their parents to participate in the research. This disqualifying criterion was not detected in any of the boys. Written informed consent was obtained from the participants when they attained 19 years of age. In addition, the participants were provided a copy of the *Certificate of Confidentiality* issued to the Center for Education and Drug Abuse Research (CEDAR) from the National Institute on Drug Abuse. Urine drug and breath alcohol screening were conducted at the outset of the experimental session to avoid obtaining results biased by substance-induced altered physiological state. None of the participants tested positive. The research protocol was administered in fixed order. At the conclusion of the evaluation the participants were debriefed and modestly compensated for their time.

Statistical Analysis

Latent growth analysis (Muthen & Muthen, 2006) was conducted to reveal the pattern of relationships among the manifest variables: transmissible risk, substance use, affect during a drug-free day, affect while under influence of a preferred drug and SUD. Mediation was investigated using the method described by Sobel (1982). Mplus software was employed using the weighted least-square parameter estimation method with diagonal weight matrix and robust standard errors.

Results

Results of the path analysis demonstrate good model-data fit ($\chi^2 = 32.46$, $df = 22$, $p = .07$; RMSEA = .040; TLI = .98; CFI = .96). As can be seen in Figure 1, affect on a drug-free day predicts frequency of consumption of preferred drugs, which in turn predicts affect while under acute drug influence and SUD. In effect, stronger *negative* affect on a drug-free day predicts higher frequency of substance consumption which predicts stronger negative affect during the consumption event. Furthermore, affect on a drug-free-day positively correlates with affect after consuming a preferred drug; that is, negative affect on an ordinary day predicts negative affect while under drug influence.

TLI intercept (outset magnitude at age 10–12) and slope (linear rate of increment in TLI from 10–22 years of age) predicts consumption frequency of preferred drugs (prodrome) and SUD (clinical disorder). TLI slope also predicts affect while under drug influence; namely, a sharper incline in the TLI during adolescence portends stronger negative affect while under drug influence. In addition, frequency of consumption of preferred drugs mediates the association of transmissible risk in late childhood (intercept) ($b = .11$, $z = 2.99$, $p = .003$) as well as its increase over time (slope) ($b = .11$, $z = 2.82$, $p = .005$) with SUD. These mediation effects respectively explain 24% and 22% of the total effect of the association between the intercept and slope leading to SUD. Furthermore, frequency of consumption of preferred drugs mediates the association of TLI intercept ($b = -.17$, $z = -3.68$, $p < .001$) and slope ($b = -.17$, $z = -3.55$, $p < .001$) and affect while under drug influence. These mediation effects respectively explain 77% and 53% of the total effect.

A second model was also examined in which the variable measuring affect on a drug-free day was deleted since it is unrelated to both transmissible risk and SUD. Results reveal satisfactory model data fit ($\chi^2 = 34.02$; $df = 20$; $p = .03$; $RMSEA = .048$; $TLI = .95$; $CFI = .97$). As can be seen in Figure 2, TLI intercept (age 10–12) and its increase up to age 22 (slope) predict frequency of consumption of preferred drugs, which in turn predicts affect while under drug influence. However, affect during the consumption event is not related to SUD. Notably, frequency of consumption of preferred drugs mediates the association of TLI intercept ($b = .13$, $z = 2.75$, $p = .006$) and slope ($b = .12$, $z = 2.62$, $p = .009$) with SUD. The mediation effects account for 28% and 25% of the total effect. Moreover, frequency of consumption of preferred drugs mediates the association of TLI intercept ($b = .29$, $z = 3.31$, $p = .001$) and slope ($b = -.19$, $z = 3.30$, $p = .001$) and affect while under drug influence. These mediation effects account for 100% and 60% of the total effect. Overall, the results indicate that affect during the drug experience is associated with frequency of consumption of preferred substances but is not related to SUD.

Discussion

This study demonstrated that frequency of consumption of preferred substances mediates the association of transmissible SUD risk during childhood and adolescence and SUD in young adulthood. Furthermore, affect on a drug-free day does not mediate the association between transmissible risk and SUD, although it predicts consumption frequency of preferred drugs which in turn predicts experienced affect during the drug use event. Whereas these findings cast a new light on the role of subjective emotional state while drug free and during the consumption event, it is important to note that affect was recorded after the intoxication experience. Hence, the possibility of biased results cannot be discounted. This potential threat to validity of the results notwithstanding, the expected pattern of association was observed. Specifically, affect on a drug-free day correlates with consumption frequency. In sum, the quality of subjective experience is not related to transmissible risk either at baseline or its increment in severity from childhood to adulthood. This finding that affect is not related to the intergenerational component of SUD risk, complemented by the observation that affect on a drug-free day is not different from affect while under influence of preferred drugs contemporaneous to SUD, adds to the growing literature indicating that self-medication is not realized by substance use (Chambers, 2013). Alternatively, it appears that cognitive and behavioral processes antedating as well as emerging consequent to substance consumption are integral to sustaining habitual consumption *despite experienced negative affect during the consumption event*. It is noteworthy in this regard that low working memory capacity (Thrush et al., 2008) and low inhibitory control (Dailey et al., 2004; Houben & Wiers, 2009) presaging first exposure to abusable substances are exacerbated by habitual drug use. Furthermore, inaccurate beliefs about the benefits of consumption of abusable compounds during adolescence mediate the association between neurobehavior disinhibition in childhood and SUD in early adulthood (Kirisici et al., 2004). Thus, while affect is a correlate of substance consumption, cognitive and motivational factors are more salient determinants of SUD.

Substance use without obtaining relief from negative affect contemporaneous to SUD is documented in the empirical literature as well as recognized by laypersons. Habitual

consumption when SUD has developed reflects a readjustment of the brain to a new state of homeostasis, termed allostatic shift (Koob & LeMoal, 2001). At this stage, substance consumption is motivated to avert onset of withdrawal syndrome. In the self-help addiction recovery movement, the concept of *chasing the dragon* is invoked to explain the reason for habitual consumption without experiencing euphoria (positive reinforcement) or abatement from aversive affect (negative reinforcement). Specifically, hazardous consumption is motivated by memories of and attempts to re-capture a positive subjective effect that was experienced during the earlier phase of substance use.

This study extends prior research demonstrating that the TLI detects children, adolescents and young adults who are at high risk for SUD. The five age-specific versions of the TLI have been adapted for administration on the Web where it is freely available (www.pitt.edu/~cedar/tlidocument.html). Considering that the TLI takes less than 10 minutes to administer and is automatically scored, it is an efficient tool for large scale screening to detect high risk youths who require intervention. Moreover, as a continuous measure of SUD risk the TLI enables ascertaining samples for research into SUD etiology by providing a specific probability ranging from 0–1 of developing SUD. Notably, the TLI is a better predictor of SUD than parental SUD+/- status (Ridenour et al., 2011). Notably, its heuristic utility has been demonstrated in several different populations besides the CEDAR sample (Arria et al., 2011; Hicks et al., 2012; Ridenour et al., 2011; Vanyukov et al., 2009). Furthermore, the findings have practical ramifications for treatment. In particular, the results suggest that focusing on improving a patient's affect may be insufficient to achieve recovery from SUD. While affective disorders commonly co-occur with SUD, the results indicate that successfully reducing substance use requires ameliorating the cognitive and behavioral factors presaging and sustaining consumption.

Several limitations of this study are noted. The finding that IQ and family socioeconomic status were somewhat lower in boys who attrited points to the possibility of biased results. However, this pattern of attrition favors obtaining negative results concomitant to the more "normal" status of the retained subjects. Also, because the sample was confined to males, the results cannot be generalized to the entire population. Females were not studied because a sex-specific version of the TLI is still under development. Also, it is important to reiterate that affect under influence of preferred drugs was measured while the participants were drug-free. Hence, the responses are not biased due to altered physiological state. On the other hand, it is possible that their retrospective reporting was not accurate despite extensive experience with each preferred drug. In addition, even though the TLI has sound psychometric properties, it is possible that additional indicator items not currently included in the index may yet be identified that further enhance its accuracy for quantifying SUD risk. Lastly, it should be emphasized that the TLI was designed to specifically measure only the intergenerational component of SUD risk. The other intra familial component of SUD risk, namely sibling influence, has no practical tool for predictive measurement. Thus, this aspect of family risk was not investigated. In addition, extra familial factors contribute to SUD risk. A provisional scale, termed the *non-transmissible index*, has been developed to quantify this component of SUD risk (Kirisici et al., 2009); however, age-specific versions have not yet been validated and, therefore, this scale was not utilized in this investigation.

Whereas sibling and extra familial factors impact SUD risk, the transmissible component measured by the TLI accounts for the largest portion of variance associated with the etiology of SUD (Hopfer et al., 2003; Vanyukov et al., 2015).

Conclusions

This prospective investigation demonstrated that consumption of preferred drugs mediates the association between transmissible SUD risk and SUD. Greater frequency of consumption of preferred drugs is also related to more severe negative affect on a drug-free day and while under acute drug influence. However, affect during the drug use event is not directly related to either transmissible risk or SUD.

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Figure 1.

Association between transmissible risk measured between childhood and adulthood, frequency of consumption of preferred drugs, drug reward and SUD.

Figure 2.

Association between transmissible risk measured between childhood and adulthood, magnitude of drug reward and SUD.

Table 1

Comparison of retained and attrited segments of the sample

	Retained (N = 301)		Attrited (N = 182)		Equivalence Test Between Groups			
	M	(SD)	M	(SD)	Difference Between Groups	95% CI for Group Difference	Probability of Equivalence	
School grade	4.56	1.13	4.52	1.01	.04	(-.16, .24)	83%	
IQ	110.22	15.88	103.53	15.22	6.69	(3.84, 9.55)	1%	
SES	41.90	13.52	39.00	12.90	2.90	(.45, 5.36)	35%	
TLI (z-score)	.19	.94	.33	1.00	.14	(-.32, .04)	99%	
	N	%	N	%				
European-American	230	76.4	135	74.2	2.2	(-5.76, 10.16)	84%	
African-American	63	20.9	39	21.4				
Other	8	2.7	8	4.4				