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Genetic relationship between the addiction diagnosis in adults and their childhood measure of addiction liability

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Abstract

Transmissible Liability Index (TLI), developed employing a high-risk design and item response theory, enables quantification of the latent trait of liability to drug use disorders (DUD) in children. TLI has been shown to have high heritability and predict DUD in young adulthood. This study extends prior research and determines the genetic contribution of DUD liability measured by TLI to adult liability as indexed by DUD diagnosis. The study utilizes data from a twin sample tracked from age 11 to age 25. In addition to confirming TLI's high heritability and predictive validity, it shows that the genetic component of variance in TLI assessed in childhood accounts for over half of the genetic variance in DUD diagnosis and the entire phenotypic relationship between the two liability measures. This validates TLI as an early measure of DUD liability and supports its utility in early-age genetic and other mechanistic studies of DUD.

Keywords

substance abuse; phenotype; measurement; males; females

Introduction

A considerable portion of variation in liability (Falconer, 1965) to substance use disorders (SUD; addictions) is nonspecific to particular drugs (Tsuang et al. 1998; Kendler et al. 2003a). As shown in twin studies, the general (common) liability mechanisms are shared at

the genetic level with antisociality/externalizing behavior (Krueger et al. 2002; Kendler et al. 2003b). As those studies estimate, this general addiction liability is significantly heritable. This trait, resulting from all non-substance-specific factors influencing addiction risk, is likely rooted in the basic mechanisms of behavior regulation, reward, affect, stress and socialization (Vanyukov et al. 2003b; Vanyukov et al. 2012; Palmer et al., 2012). As many other complex (multifactorial) traits, individual variation in which is determined by numerous organismic and environmental factors, addiction liability is likely a continuous trait and has a normal phenotypic distribution in the population, as per the central limit theorem.

Because addiction liability is a latent trait (unobservable; not directly measurable), its individual assessment, needed for etiological research as well as for tracking changes in the risk for and severity of the disorder, is fraught with complexities. The individual behavioral phenotype and the addiction liability phenotype in particular are dynamic and labile – because of their general ontogenesis and due to the impact of person-specific salient factors that influence their development throughout lifetime. Practical medical needs have required a categorical diagnosis of the disease, as opposed to phenotypic approaches in other areas, e.g., psychology, where latent traits are largely quantified using dimensional indices (e.g., IQ). The dichotomous diagnostic definition of the addiction liability phenotype, which collapses the continuous liability distribution in the population into two discrete classes, incurs information loss and thus is not optimal from an analytic standpoint. The diagnostic criteria for addiction (and other behavioral disorders) are nonuniform, comprising hundreds of symptom combinations, and vary across time and populations. In addition, in the unaffected and particularly asymptomatic individuals, including children, the absence of the face-value indicators of the disorder precludes the diagnosis-based specific examination of the relationships of addiction liability with any mechanistic variables. This particularly concerns biological mechanisms, such as the effects of genetic polymorphisms, each of which, if associated with addiction liability, likely contributes only a small proportion to the phenotypic variation. The detection of those small effects, difficult as it, is further complicated by the need to correct for the Type 1 error inflation ensuing from the large number of tests required, e.g., in genome-wide association studies. Moreover, because SUD liability phenotype, studied at the relatively late age when the disorder manifests, is the result of a long developmental process, the effects of early acting factors, mediated and moderated by numerous intervening variables, are weakened.

To alleviate these problems, it seems important to augment clinical diagnoses with dimensional indices of liability (Vanyukov et al. 1993; Vanyukov and Tarter 2000; Iacono et al. 2009; Conway et al. 2010), particularly covering asymptomatic individuals as well as those too young to have an opportunity to be exposed to the pathogen, i.e., drugs. Consistent with the continuous SUD risk-severity variation (Fulkerson et al. 1999; Hartman et al. 2008), including its continuity across adolescence and adulthood (Baker et al. 2011; Vrieze et al. 2012), these indices may cover both risk and severity areas of the liability distribution (i.e., under and above the diagnostic threshold). The practical application of such indices could provide guidance to intervention and outcome evaluation, including: individually-tailored primary prevention, via identifying persons at measured elevated risk; individually-

tailored patient-treatment matching and longitudinal tracking of the outcome; and a direct mapping between research studies and clinical practice.

As shown in prior research, SUD liability can be dimensionally quantified in children by applying a high-risk/family paradigm to derive a transmissible liability index (TLI) (Vanyukov and Tarter 2000; Vanyukov et al. 2003a,c; 2009; Kirisci et al. 2009, 2012). The transmissibility concept is based on the model partitioning liability variance into two components, transmissible (correlated between parents and offspring) and nontransmissible (tau model; Rice et al. 1980; Vanyukov et al. 2003b), which is amenable to analysis in nuclear (non-twin) family data. Inasmuch as SUD liability is transmissible between generations (e.g., due to its significant heritability), behavioral/psychological characteristics that discriminate between groups of children with affected and unaffected parents are likely to be indicators of children's own transmissible SUD liability. These characteristics are assessed by item sets comprising psychological and diagnostic questionnaires.

Selecting items in this manner, whereby the predominant source of the relationship between them is SUD liability, has ensured the unidimensionality of the trait (a considerable proportion of response variance, > 20%, is accounted for by a single factor [Reckase, 1979]) and the local independence of the items, the testable conditions for their analysis by item response theory (IRT) methods. IRT (e.g., Embretson and Reise 2000) provides models that relate responses to individual items (e.g., in a psychological questionnaire) to the latent trait underlying their variation. This relationship (in a simple case, between the trait and the probability of a correct response) is described by an item response function (IRF). While the trait level is a characteristic of the examinee, performance also depends on the parameters characterizing items themselves. For instance, in the widely used two-parameter logistic model, these are the location (difficulty, or threshold) parameter (b ; the trait value at which the probability of a correct response exceeds 0.5), and the discrimination parameter (a ; proportional to the slope of the IRF at the point b on the trait scale). These parameters take into account that different items differ in (i) their rates of endorsement and (ii) their ability to discriminate between the values of the trait (i.e., individual phenotypes). IRT derivation results in the index that places individual scores on the same scale irrespective of the sample and the subset of items used (the group and item parameter invariance characteristics of IRT).

In addition to satisfying the usual validity criteria, and consistent with TLI's theoretical relationship with the transmissible component of liability variance, the index has been shown to be highly heritable (Vanyukov et al. 2009). This result has been confirmed in a sample of twins from the Minnesota Twin and Family Research Center (MCTFR) (Hicks et al. 2012). In that latter study, however, rather than applying IRT for scoring, responses to TLI items were used to calculate their mean z-score (a sum of the z-scores of each TLI item's responses, weighted by the number of valid responses by the individual). An IRT analysis of the data might allow taking full advantage of the TLI derivation methodology. The Hicks et al. study also established a substantial genetic correlation between that score and the children's SUD outcome by age 17, accounting for over 90% of the phenotypic correlation. It is plausible for this correlation to be interpreted in directional terms: because TLI is a measure of SUD liability *in childhood*, TLI's heritability should account for the

genetic relationship between TLI and the *adult* categorical diagnosis of addiction. In other words, the heritability of TLI should pertain specifically to the heritability of SUD liability rather than of other traits with which it may be associated at the genetic level, and thus TLI should indeed index SUD liability in childhood. Hence, confirming this interpretation would be consistent with TLI's ability to evaluate the heritable component of SUD liability before the person's reaching the age when an SUD diagnosis, which remains the main criterion variable, can be made. This would support the utility of TLI in molecular genetic and other mechanistic early-age studies of SUD.

Methods

Participants

The study analyzed data from the sample of 394 monozygotic (MZ) and 221 dizygotic (DZ) same-sex pairs of male twins, and 390 MZ and 250 DZ pairs of female twins from the Minnesota Center for Twin and Family Research, MCTFR (Iacono et al. 1999). Mean ages at each assessment are presented in Table I. Zygosity was determined by the agreement of a standard questionnaire completed by parents, evaluation of physical similarity by MCTFR staff, and an algorithm assessing the twin similarity on ponderal and cephalic indices and fingerprint ridge counts (Hicks et al. 2012). These individuals entered the study at age ~11, and to be eligible for SUD and bivariate analyses had to be through at least the fifth assessment, age on average 24.3 ± 0.05 , ranging 23.7–27.8 (thus differing from the age of 17 in Hicks et al. [2012]). This ensures that a larger proportion of the sample have passed through the age of SUD risk, preventing underdiagnosing of presumably unaffected individuals. The DSM-III-R diagnostic assessments for SUD were conducted according to the Substance Abuse Module of the Composite International Diagnostic Interview (Robins et al. 1987). The members of the twin pairs were interviewed separately and concurrently. The prevalence of substance use disorders at each age (starting at 17) is presented in Table II.

While SUD related to licit and illicit substances are frequently comorbid, liabilities to them have been shown to form two genetically distinct, albeit correlated, groups – likely due to differences in underlying psychological characteristics needed to overcome societal barriers for involvement with licit and illicit substances (Kendler et al. 2007). TLI was developed specifically to index general (common) liability to disorders related to illicit drugs (drug use disorders, DUD). To take that into account, the diagnoses of alcohol use disorder and/or nicotine dependence only were not sufficient to qualify for the affected status in this study. At the same time, allowing alcohol use disorders as a characteristic of the unaffected phenotype would be unreasonable, while the genetic variance of liability to nicotine dependence is known to be largely substance-specific and share relatively little variance in common with the “illicit” genetic factor (Kendler et al., 2007). Therefore, the affected status was assigned based on the presence of a lifetime (by the age of the fifth assessment) DSM-III-R diagnosis of abuse of/dependence on an illicit (or used without a prescription) substance, including “probable” diagnoses (one symptom short of the usual diagnostic threshold) to take into account common underreporting of SUD symptoms (Takayanagi et al. 2014). The unaffected status was assigned based on the absence of both illicit drug-

related and alcohol use disorders. The data for the entire sample were available for the TLI univariate analyses. For lifetime SUD diagnosis-related analyses, data on 135 MZ and 64 DZ male pairs, and 144 MZ and 79 DZ female pairs were available.

Analysis

TLI—TLI has been originally developed in the Center for Education and Drug Abuse Research (CEDAR), and its rationale and derivation procedure have been described in detail elsewhere (Vanyukov and Tarter 2000; Vanyukov et al. 2003a,c; Vanyukov et al. 2009, the latter article contains the full list of TLI items). Briefly, a large set of items from numerous psychological and psychiatric instruments, selected in CEDAR based on their potential for measuring variables related to SUD risk and psychopathology, were submitted to conceptual, factor and item response theory (IRT) analysis to derive theoretically based unidimensional constructs characterizing individual behavior/personality. The groups of children whose fathers were either affected with a DSM-III-R drug use disorder, DUD (related to any illicit substance), or had no psychiatric disorder were then compared on these constructs derived based on assessments conducted at the first visit (children's age ~11). The items that were indicators of the constructs differentiating between the two groups were then submitted to factor analysis and, upon establishing the unidimensionality of the underlying construct, to IRT analysis for calibration and index scoring.

TLI items, using mothers', teachers' and children's reporting at the same children's age as in CEDAR, ~11, were previously identified in the MCTFR data dictionary (Hicks et al. 2012). In contrast to that prior work in that dataset, IRT scoring was applied to TLI items in the current study. Two sets of scores were derived. One was based on the application of the item parameters estimated in item calibration in the CEDAR sample (Vanyukov et al. 2009). The other set was based on item parameter estimation in the MCFTR data. IRT analysis was conducted using MPlus. A graded response model (Samejima 1969) was applied to this mixed-format item set (differing numbers of response categories in different items). There were 20 TLI items available in the MCTFR dataset. In a single case where the number of response categories in the item differed between the studies—three in CEDAR but four in MCTFR, - the categories were combined to reduce the number to three, as in CEDAR. The TLI scores are standardized.

Twin analysis—Standard univariate models were employed to estimate phenotypic variance components for TLI and the binary DUD diagnosis in the twins. These models commonly include the additive genetic component (A; due to the additive genetic effects originating from the differences between the alternative homozygotes), the nonshared (or unique) environment component (E; due to the nongenetic sources of intrapair dissimilarity and measurement error), and, alternatively, shared (or common) environment (C; due to the nongenetic sources of intrapair similarity) or dominance genetic component (D; due to the differences of heterozygotes from the mean of the homozygotes). In twins raised together, it is not possible to model simultaneously the C and D contributions, because the former decreases and the latter increases differences between MZ and DZ intrapair correlations (e.g., Neale and Cardon 1992). Accordingly, the initial model to fit, which includes only one of these components, either C or D, is selected based on whether the MZ correlation is less

or greater than twice the DZ correlation – ACE or ADE, respectively. The former case prefers the presence of the shared environmental component, whereas the latter, the presence of the dominance genetic component. The estimate of narrow sense heritability, the proportion of phenotypic variance due to the additive genetic component (A), is denoted h^2 or a^2 .

Raw data, and variance–covariance and correlation matrices were used for structural equation model fitting, as described in the Results. The χ^2 (likelihood ratio) statistics, Akaike Information Criterion (AIC), as well as the root mean square error of approximation (RMSEA) were used as fit and comparative fit indices. A nonsignificant χ^2 value for a model and $RMSEA < .05$ indicate good fit, and a lower AIC value corresponds to a more parsimonious model (compared to χ^2 , AIC penalizes for the number of free, estimated, parameters in the model). Nested models (differing in that parameters present in one, more general, model are equated in or omitted from another, reduced, model) can be compared by evaluating the difference of a χ^2 values of the two models. Under certain regularity conditions, this difference statistic is asymptotically distributed as χ^2 , with degrees of freedom equal to the difference between the numbers of degrees of freedom in the two models. Based on model fit and the path's significance, the nested models may omit (“drop”) any variance component except for E (the measurement error is always present) in both ACE and ADE models, and also except A in the ADE model because the DE model is biologically implausible.

The univariate analysis was employed to both evaluate the model parameters for each of the variables and to select the plausible initial model for the bivariate analysis, relating the childhood TLI and the young adult's categorical diagnosis. The models were fitted by maximum likelihood using Mx software (Neale et al. 2003). The p -values for the goodness–of-fit likelihood-ratio test comparisons of univariate models, reported by Mx, were halved (Dominicus et al. 2006; Wu and Neale 2012; Wu and Neale 2013). Descriptive statistics, odds ratios (OR) and correlations with their confidence intervals were estimated using SPSS version 21 (IBM, 2012), Stata version 12 (Stata Corp, 2013), and G*Power 3.1.7 (Faul et al. 2009).

Results

TLI phenotyping

Scoring the MCTFR sample based on item parameters from item calibration in the MCTFR and CEDAR samples arrives to highly convergent results: correlations between the TLI scores obtained applying the CEDAR- and MCTFR-derived parameters are > 0.9 (Pearson $r = 0.91$; Spearman $\rho = 0.95$). The point-biserial correlations of the two indices with the DUD diagnosis did not differ significantly from each other and between sexes: in males, for MCTFR- and CEDAR-derived scoring, respectively, 0.245 and 0.272, and in females, 0.281 and 0.279 (all correlation coefficients were highly significant, $p \ll .001$). In the entire sample, the respective correlations for the two indices with the diagnosis were 0.291 and 0.325, again not differing significantly ($p = .37$). In logistic regression, both MCTFR- and CEDAR-derived scores similarly predicted DUD, $OR = 2.55$ (95% CI: 2.10–3.11) and

OR=2.62 (2.19–3.15). Therefore, for consistency with prior research, the TLI scores based on CEDAR-derived item parameters were used for further analysis.

Univariate phenotypic variance analysis

Univariate (intraclass for TLI and tetrachoric for the DUD diagnosis) and bivariate (point-biserial) correlations within twin pairs are summarized in Table III. The intraclass TLI correlations (as variance ratios, they are indifferent to the assigned order in the twin pair) did not differ significantly between males and females: in MZ male and female twin pairs they were, respectively, 0.721 (95% CI: 0.670–0.765) and 0.686 (0.629–0.735); and in DZ twins, 0.363 (0.243–0.472), and 0.264 (0.145–0.376). The MZ and DZ TLI correlations significantly differed within each sex, whereas there were no significant differences between sexes within the zygosity.

For DUD, tetrachoric correlations in MZ male and female twin pairs were, respectively, 0.903 (0.819–0.987) and 0.806 (0.674–0.938), and in DZ pairs, 0.824 (0.642–1.000) and 0.618 (0.627–0.903). Within the zygosity, male and female correlations do not differ significantly. MZ and DZ differences are not significant as well, albeit there is an apparent trend for MZ correlations to be higher.

Table IV presents the results of univariate model analyses. For TLI, ADE is selected as the initial model in both males and females: in males, because r_{MZ} is almost exactly twice r_{DZ} , selecting the ACE or ADE model is unlikely to influence the result (a priori likely corresponding to an AE variance structure); whereas in females $r_{MZ} > 2r_{DZ}$, justifying the ADE choice. Supporting prior results, TLI is highly heritable in males, $h^2=0.72$ (95% CI: 0.67–0.76), with twin resemblance entirely accounted for by additive genetic factors. In females, although the full ADE model fits slightly better, both A and D components include 0 in their 95% confidence intervals, although the model with both genetic components omitted fails (consistent with the CI for E not including 1). Thus, the composition of phenotypic variance in females is estimated to be very similar to that in males: $h^2=0.69$ (0.63–0.74). The combined sample's estimates for TLI are $h^2=0.72$ (0.69–0.75) and $e^2=0.28$ (0.25–0.31).

For liability to DUD as manifest in the lifetime diagnosis by age ~25 years, the initial model in males is ACE. The difference between the tetrachoric correlations in MZ and DZ pairs does not reach significance and suggests a prominent shared environment component: 0.90 (95% CI: 0.819–0.987) vs. 0.82 (0.642–1.000). Accordingly, there is no significant difference in fitting the ACE and CE models to the raw (contingency table) data. The estimate for a^2 is 0.14, with a confidence interval that includes 0 (0–0.67), suggesting that the reduced, CE, model is sufficient to account for the composition of the phenotypic variance: $c^2=0.87$ (0.77–0.94); $e^2=0.13$ (0.06–0.23). The CE model is also best-fitting ($p=.602$; AIC=−5.258; RMSEA < .001). The AE model fits worse ($p=.057$; AIC=1.191; RMSEA=.085), and significantly worse than the full model ($p=.008$). Inasmuch as the direction of the MZ-DZ difference in correlations, albeit nonsignificant, is consistent with that expected when genetic variation does play a role, it is possible, however, that the lack of significance for the genetic component is due to insufficient statistical power.

In females, ACE is assumed as the initial model as well: $r_{MZ} < 2r_{DZ}$. Although the difference between MZ and DZ DUD correlations is greater than in males, it is still nonsignificant: 0.81 (0.673–0.938) vs. 0.62 (0.357–0.879). Although the full model fits to the raw data well, both A and C component estimates are nonsignificant, 0.43 (0–0.88) and 0.39 (0–0.82), whereas the model cannot be reduced to the E model. The AE model provides equally good fit (a nonsignificant χ^2 difference from the ACE model), with A and E estimates of 0.82 (0.67–0.92) and 0.17 (0.08–0.32). The CE model's fit is only slightly worse than that for the AE model. Neither reduced model improves fit compared to the full model. Whereas the fits of the ACE, AE and CE models do not differ significantly, it does not appear reasonable to drop either A or C component, considering the MZ and DZ correlations.

The lack of significant sex differences in twin correlations prompts the evaluation of the possibility of analyzing male and female pairs conjointly, testing for sex heterogeneity. Fit improvement for the model equating the respective variance components in males and females is not significant, and parsimony prefers this model over sex heterogeneity (AIC improves from –8.062 to –9.016). The A, C, and E component estimates are, respectively, 0.28 (0–0.70), 0.56 (0.16–0.84), and 0.14 (0.08–0.23).

Bivariate analysis

Because of the developmental relationship between TLI, measured in children, and the DUD diagnosis, determined in the same individuals as adults, the bivariate modeling relating these variables affords interpretation in directional ontogenetic terms. TLI is theorized to be a measure of DUD liability at childhood, at an earlier period of the trait's development, whereas the diagnosis is the trait's measure at adulthood. Thus, testing if the genetic component of TLI variance accounts for covariation between these two variables evaluates the utility of TLI as an early measure of DUD liability at the genetic level. The absence of significant sex heterogeneity in both variables justifies joining the male and female samples for bivariate analyses.

As illustrated in Fig. 1, the relationship between the two liability measures can be modeled in two alternative ways: at the phenotypic level – via connecting the observed variables by a direct path (Model 1), and at the latent variance components level (Model 2; the Cholesky model [e.g., Neale and Cardon 1992]). Both models would evaluate the degree to which addiction liability indexed by TLI accounts for the later measurement of addiction liability, indexed by the categorical diagnosis. Whereas the Cholesky model itself generally does not constrain the directionality of a phenotypic relationship, in this case the model is reflective of a developmental process and a priori consistent with the temporal ordering of the data. The results of testing these two modeling alternatives and their respective nested models are presented (Table V present the fit comparison; and Table VI, the parameter estimates for the best-fitting model).

Full initial Model 1 does not provide a good fit to the data ($p = .007$; RMSEA=.058). Because the common environmental component, lacking in TLI's variance, thus cannot be shared between the two variables, the only model component that could be reasonably

attempted to be dropped is the diagnosis-specific additive genetic variance, A_{DUD} (Model 1a). That, however, results in further fit deterioration.

The Cholesky model appears to provide better solutions than Model 1. Full Model 2 fits well ($p=.325$). The $E_{TLI-DUD}$ path, corresponding to the contribution of the nonshared environment variance component of TLI to the variation in the diagnostic outcome, however, is estimated as nonsignificant. Omitting this path (Model 2a) results in the model parameters indicating a significant contribution of the genetic variance of TLI to the DUD realized risk variation, comprising over half of the latter's genetic variance and 18% of its phenotypic variance: $A_{TLI \rightarrow DUD} \beta=0.43$ [95% CI: 0.35–0.510]). The genetic relationship, estimated by the genetic correlation of 0.36, is the only source of correlation between the two measures of DUD liability. Dropping the A_{DUD} component (genetic variance specific to liability indexed by the diagnosis; Model 2b) leads to significant deterioration of fit ($p<.05$), leaving Model 2a as the best-fitting.

Discussion

This study is an extension of research in developing and validating quantitative measures of liability to SUD. The need for dimensional measures that would be consistent with the theoretically continuous variation in liabilities to complex disorders (e.g., psychiatric and behavioral) has long been established – from the description of liability as a trait (Falconer, 1965) to the development of indices of this latent trait for addiction research (Vanyukov et al. 1993; Vanyukov and Tarter 2000; Vanyukov et al. 2003c; Conway et al 2010). This need has recently been recognized by the National Institute of Mental Health in setting the goal to “[d]evelop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures” (NIMH 2011), while pursuing a somewhat different perspective in that direction¹.

The quantification of the target phenotype is important for several practical reasons, including, most obviously, possible gains in statistical power that are afforded by employing continuous rather than dichotomous variables. This is especially important when it concerns the criterion variable, the one whose variation is the focus of the study. Research into mechanisms is using increasingly more precisely measured explanatory characteristics, such as those of the genetic sequence, epigenetic patterns, gene expression, and various quantitative biochemical and physiological parameters. In contrast, the categorical diagnosis with its imprecision, arbitrariness and inability to differentiate the phenotypes *within* the diagnostic groupings, is a bottleneck limiting the effectiveness of research. Despite that, however, there are few studies that aim at quantitatively indexing liability to addiction, and TLI is currently the only such index for children that is part of the PhenX database toolkit, the complex trait phenotyping initiative funded by the National Human Genome Research Institute (Hamilton et al. 2011).

¹In the NIMH approach, the neurobiological mechanisms are supposed to “inform” the Research Domain Criteria (RDoC), which renders those mechanisms effectively subsumed under the RDoC. In the liability index approach, as employed, e.g. in the development of TLI, the phenotype remains at the same psychological/behavioral level of biological organization as the disorder diagnosis, which allows studying mechanisms as independent variables while augmenting the diagnostic classification.

This study confirmed the results of the univariate analyses of TLI variance composition in both CEDAR dataset (Vanyukov et al. 2009) and in the MCTFR (Hicks et al. 2012). The heritability estimates are high, consistent with the theoretical foundation and derivation of TLI as an index of transmissible liability to DUD, as well as virtually identical to those obtained before. The only source of intrapair twin similarity for TLI is additive genetic, with no significant sex differences. The estimates for univariate DUD models are within the range reported in the literature (Hopfer et al. 2003).

The key findings of this study pertain to the results of bivariate analyses. Consistent with the study's hypothesis that TLI indexes the transmissible (primarily, heritable) component of addiction liability, the relationship between TLI in childhood and the DUD diagnosis in adulthood is entirely accounted for by the genetic variance of TLI, supporting the Hicks et al. (2012) findings. The genetic correlation is estimated as virtually the same as in the Hicks et al. study (0.36 vs. 0.39), despite the differences in SUD measurement. The effect size is moderate, which might be interpreted as weakening the utility of the index. It should be noted, however, that it would be unreasonable to expect a behavioral variable in childhood to be strongly predictive of adult behavior, particularly when the measurement is heteronymous (using two different metrics, TLI and the diagnosis), and the trait is inherently labile and undergoes complex nonlinear ontogenesis (Vanyukov and Tarter 2000). For instance, even for IQ, an index of intelligence that is considered relatively stable – to the degree that it is used for assigning children to school programs determining their future development, — variation in its values at age 10 accounts for less than 50% of variance in verbal and less than 40% in nonverbal abilities at age 18 (Hoekstra et al. 2007). This evaluation of the index's *predictive* strength does not, however, necessarily mirror the value of its early-age-specific *measurement*, just as body mass measurement in childhood has its own utility regardless of what it will be in adulthood. In fact, inasmuch as the elevated TLI values are reflective of social (mal)adaptation mechanisms, it is conceivable that the behavior correction influences during the child's upbringing, which are directed at modifying and adjusting behavior at the higher end of the distribution, may result in the erosion of the relationship. The sample also has not yet entirely passed through the age of risk for DUD, whereas it is expected that the lower TLI values are associated not only with a lower DUD risk but also with later disorder onset (Vanyukov et al. 2009). The measurement precision of TLI is also lower (the error is greater) at its lower values, as TLI items are largely indicators of behavioral problems. In addition, to ensure generalizability of the parameter estimates, the results warrant replication in a larger sample tracked to a later age.

These caveats notwithstanding, the data support TLI's utility for early access to the genetic component of DUD liability variance for association and other mechanistic research - before the development of any DUD symptoms and even drug use. TLI is confirmed to be highly heritable, with additive genetic mechanisms accounting for the phenotypic resemblance in twin pairs. The genetic variance of TLI captures a significant amount of the genetic variance of adult DUD liability, with the genetic correlation between TLI and the diagnosis accounting for the entire phenotypic relationship.

To be sure, the considerable heritability of TLI, an early measure of liability to addiction, does not mean that the trait is "genetic" in the sense of inability to change under an external

(environmental) influence. Rather, the high heritability of TLI indicates that under the current conditions, in the population from which the twin sample was drawn, genetic variation accounts for a large part (but not entirety) of individual differences in this variable – an index of a developmental and malleable behavioral trait. This population estimate has no direct relevance to a particular individual phenotype, nor to the prognosis of the effect of an environmental factor (e.g. a prevention intervention) if it is introduced at the individual or population level. Indeed, a TLI estimate of high addiction liability could potentially provide a timely indicator for intervention.

The development of dimensional liability measures, currently underway and based on TLI methodology but relying entirely on the individuals' own (rather than including parental diagnostic) data, and covering the full extent of the distribution of liability phenotypes both in childhood and adulthood, is likely to improve the precision of measurement of both phenotypic and genetic characteristics of addiction liability. This will benefit intervention, assisting individually-oriented prevention and treatment, as well as research, providing adequate criterion variables.

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Figure 1.
Bivariate models (see description in the text)

Table 1

Mean ages (SD) of participants at consecutive assessments

Sex	Zygosity	Visit				
		1	2	3	4	5
Male	MZ	11.8 (0.41)	14.9 (0.52)	18.0 (0.60)	21.9 (0.72)	25.3 (0.70)
	DZ	11.8 (0.52)	14.9 (0.47)	18.0 (0.56)	21.9 (0.76)	25.3 (0.70)
Female	MZ	11.8 (0.48)	14.9 (0.61)	18.1 (0.65)	20.9 (0.59)	25.2 (0.76)
	DZ	11.8 (0.43)	15.0 (0.59)	18.2 (0.67)	21.0 (0.60)	25.3 (0.70)

Table II

Prevalences of alcohol abuse/dependence, nicotine dependence, and any illicit substance dependence

Sex	Zygosity	Age							
		17			20			24	
		Alcohol	Nicotine	Illicit	Alcohol	Nicotine	Illicit	Alcohol	Illicit
Males	MZ	33.6	22.0	17.3	46.9	22.0	17.9	41.9	10.7
	DZ	31.5	17.6	16.5	48.2	19.7	19.2	35.5	12.9
Females	MZ	12.5	10.5	7.2	13.5	12.2	6.5	15.0	5.4
	DZ	17.4	17.4	10.4	19.8	14.4	9.6	20.4	6.6
									17.8

Table IIITwin correlations^a

Phenotype (twin in the pair)	TLI1	DUD1	TLI2	DUD2
TLI1	1	.215/.253	.686/.264	.130/.214
DUD1	.235/.378	1	.231/-.004	.806/.618
TLI2	.721/.363	.234/.256	1	.206/.407
DUD2	.232/.283	.903/.824	.232/.319	1

^a Numbers after the variable name mean the twin in the pair; females above, males below the diagonal; first value in the cell is MZ, second, DZ

Table IV

Univariate model parameters

Sample	Model	χ^2	df	P	AIC	χ^2	df	P	RMSEA	Model parameters (95% CI)		
										TLI		
										a^2	d^2	e^2
Male	ADE	0.699	3	0.873	-5.301				0.000	0.72 (0.28-0.76)	0.00 (0.00-0.44)	0.28 (0.24-0.33)
	AE	0.699	4	0.951	-7.301	0.000	1	.5	0.000	0.72 (0.67-0.77)		0.28 (0.24-0.33)
	E	319.189	5	<0.001	309.189	314.489	2	<0.001	0.384			1.00 (1.00-1.00)
Female	ADE	5.849	3	0.119	-0.151				0.047	0.31 (0.00-0.71)	0.39 (0.00-0.73)	0.30 (0.26-0.35)
	AE	9.250	4	0.055	1.250	3.401	1	0.03	0.054	0.69 (0.64-0.74)		0.31 (0.26-0.36)
	E	270.221	5	<0.001	260.221	264.372	2	<0.001	0.342			1.00 (1.00-1.00)
Full	ADE	2.860	3	0.414	-3.140				0.018	0.63 (0.30-0.75)	0.09 (0.00-0.42)	0.28 (0.25-0.31)
	AE	3.206	4	0.524	-4.794	0.346	1	0.279	0.014	0.71 (0.69-0.75)		0.28 (0.25-0.31)
	E	633.059	5	<0.001	623.059	630.199	2	<0.001	0.380			1.00 (1.00-1.00)
DUD												
Male	ACE	2.171	3	0.538	-3.829				0.007	0.14 (0.00-0.67)	0.75 (0.24-0.93)	0.10 (0.04-0.22)
	AE	9.191	4	0.057	1.191	7.020	1	0.004	0.085	0.91 (0.81-0.96)		0.09 (0.04-0.19)
	CE	2.742	4	0.602	-5.258	0.572	1	0.225	0.000		0.87 (0.77-0.93)	0.13 (0.06-0.23)
	E	93.909	5	<0.001	91.738	83.909	2	<0.001	0.370			1.00 (1.00-1.00)
Female	ACE	1.767	3	0.622	-4.233				0.000	0.41 (0.00-0.90)	0.38 (0.00-0.81)	0.19 (0.09-0.36)
	AE	3.345	4	0.486	-4.555	1.677	1	0.098	0.028	0.82 (0.68-0.92)		0.18 (0.08-0.32)
	CE	3.940	4	0.414	-4.060	2.172	1	0.071	0.022		0.74 (0.59-0.85)	0.26 (0.15-0.41)

Sample	Model	χ^2	df	P	AIC	χ^2	df	P	RMSEA	Model parameters (95% CI)	e^2
No sex heterogeneity											
	E	62.164	5	<0.001	52.164	60.397	2	<0.001	0.272		1.00 (1.00–1.00)
	ACE	6.984	8	0.538	−9.016	3.046	2	0.218	0.000	0.29 (0.00–0.70)	0.57 (0.17–0.84)
	AE	14.095	9	0.119	−3.905	10.157	3	0.009	0.039	0.87 (0.79–0.93)	0.15 (0.08–0.24)
	CE	9.896	9	0.359	−8.104	5.958	3	0.057	0.038	0.81 (0.72–0.87)	0.13 (0.07–0.21)
	E	156.073	10	<0.001	136.073	152.135	4	<0.001	0.307		0.19 (0.13–0.28)
											1.00 (1.00–1.00)

Table V

Bivariate model fit tests

Model	χ^2	df	P	AIC	$\delta\chi^2$	δdf	P δ	RMSEA
1	36.22	18	0.007	0.224				0.058
1a	112.06	19	<.001	74.045	75.84	1	<.0001	0.143
2	19.07	17	0.325	-14.932				0.036
2a	20.76	18	0.291	-15.236	1.69	1	>.01	0.031
2b	28.81	19	0.069	-9.188	9.74	2	<.001	0.040

Table VI

Best-fitting model parameters

Paths	β (95% CI)	Variance decomposition
$A_{TLI} \rightarrow TLI$	.84 (.81, .87)	.71 (.66, .76)
$E_{TLI} \rightarrow TLI$	.53 (.49, .58)	.29 (.24, .34)
$A_{TLI} \rightarrow DUD$	.43 (.35, .51)	.18 (.12, .26)
$A_{DUD} \rightarrow DUD$	.38 (.21, .53)	.14 (.04, .28)
$C_{DUD} \rightarrow DUD$	.74 (.64, .81)	.55 (.41, .66)
$E_{DUD} \rightarrow DUD$	.34 (.31, .37)	.12 (.10, .14)