Familiality of addiction and its developmental mechanisms in girls

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ABSTRACT

Background: Drug use disorders (DUD) have been theorized to share sources of risk variation with other consummatory behaviors. We hypothesized that common mechanisms exist for familial risk for DUD, physiological maturation and nutritional status in girls. Whereas body fat content must exceed a threshold to enable adrenarche and gonadarche, nutritional status may also be a behavior risk indicator. Impaired psychological self-regulation associated with DUD risk may manifest in early overeating, which could in turn accelerate reproductive maturation, resulting in a greater likelihood of affiliation with deviant/older peers and drug use.

Method: The sample consisted of families ascertained through the father who either had ($N = 95$) or did not have ($N = 130$) a DUD, and who had a 10–12 year old daughter and her mother available for study. Correlation, survival and path analyses of three consecutive assessments evaluated the relationships between parental DUD (number of affected parents, NAP), nutritional status (NS, subscapular skinfold measurements and body mass index), sexual maturation (Tanner stage), peer delinquency, and the daughter's lifetime DUD diagnosis.

Results: NAP was positively related to the girls' nutritional status. Longitudinal path analysis indicated mediation of the relationship between NAP and peer delinquency by sexual maturation. The relationship between NAP and sexual maturation is mediated by NS. The effect of sexual maturation at age ∼11 on the girls' DUD risk is mediated by peer delinquency.

Conclusion: The data are consistent with mediation of intergenerational transmission of DUD risk in females by elevated nutrition, leading to accelerated maturation, and affiliation with deviant peers.

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1. Introduction

Drug addictions (drug use disorders, DUD) have been theorized to share mechanisms of risk variation with other consummatory behaviors (Vanyukov et al., 2012). These mechanisms span all levels of biological organization and may differ between sexes. It has been previously shown that parental addiction to illicit drugs is related to the rate of sexual maturation in male offspring, which in turn is associated with their disruptive behavior, peer delinquency, and risk for DUD (Kirillova et al., 2001, 2008). Extending this line of research, we hypothesized that common mechanisms also exist for familial risk for DUD, physiological maturation and nutritional status in girls. Disordered eating behavior and the risk for drug addiction are known to be phenotypically correlated. For example, bulimia, which is particularly prevalent among

females, is frequently comorbid with substance use disorders, and the relationship extends to positive genetic correlations between symptoms of bulimia and addictions (Baker et al., 2010; Trace et al., 2013). Moreover, family history of addiction—alcoholism in parents, which is frequently comorbid with other substance use disorders—has been found to be related to obesity in their offspring (Grucza et al., 2010). Whereas body fat content in females must exceed a certain level to enable adrenarche and gonadarche, nutritional status that does not necessarily reach the diagnostic threshold of an eating disorder may also be an indicator of behavioral risk and contribute to its further increase. In particular, impaired psychological self-regulation, likely to a degree underlying DUD risk, may manifest in early-onset overeating and accumulation of fat, which could in turn increase the rate of reproductive maturation, resulting in a greater likelihood of affiliation with deviant/older peers and drug use. Accordingly, nutritional status, as reflected in adiposity, may mediate the relationship between parental DUD and, developmentally, daughters' physiological maturation, peer affiliation and DUD. In this study, we tested this system of relationships, illustrated in Fig. 1.

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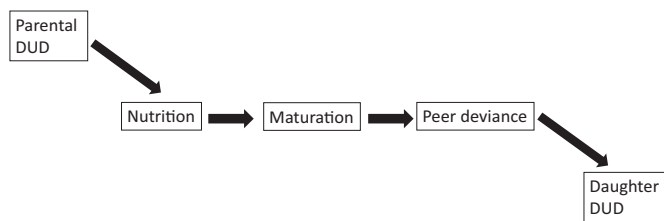*E-mail address:* galinag@pitt.edu (G. Kirillova).

Fig. 1. The hypothesized pathway of addiction liability transmission.

2. Method

2.1. Participants

The sample, part of a longitudinal family/high-risk study (Center for Education and Drug Abuse Research, CEDAR; Tarter and Vanyukov, 2001), consisted of 225 families ascertained through the father who either had ($N = 95$) or did not have ($N = 130$) a lifetime DSM-III-R diagnosis of drug use disorder (DUD; abuse and/or dependence) related to an illicit drug(s) (alcohol dependence only did not qualify), and who had a ~10–12 year old biological daughter (index child, IC) and her biological mother available for study. Control fathers had no Axis I or II psychiatric disorder. A DSM-III-R diagnosis was used because DSM-IV was introduced after this study started. The girls were self-identified as European-American (71%), African-American (27%), or "other" (2%). Recruitment was via newspaper advertisements, social service agencies, substance abuse treatment programs and various other media. The family was excluded if the father had a history of neurological disorders, schizophrenia or uncorrectable sensory incapacity, or the IC had a history of neurological injury requiring hospitalization, IQ less than 80, chronic physical disability, uncorrectable sensory incapacity or psychosis. The girls are prospectively assessed at regular intervals. For all variables, except the girls' DUD diagnosis, data from the first three assessment visits were used in this study. In order to capture the maximal information on the main outcome variable, lifetime DUD diagnosis by the *last available* visit for the individual was used. The girls' age statistics are presented in Table 1. Because of protracted recruitment, the diminishing sample sizes at the follow-up visits do not per se indicate attrition. Prior analysis in the sample suggests no systematic attrition bias (Kirisci et al., 2012).

This study was reviewed and approved by the Institutional Review Board of the University of Pittsburgh. Adult participants provided written informed consent prior to implementing the research protocol. Children provided assent and, upon reaching age 18, informed consent.

2.2. Instrumentation

2.2.1. Psychiatric diagnosis.
An expanded version of the Structured Clinical Interview for DSM-III-R-outpatient version (SCID-OP; Spitzer et al., 1987) was administered by experienced research associates to obtain psychiatric diagnoses for adults. The expanded SCID evaluates current episode (past 6 months) and worst past episode of psychopathology (before the past 6 months). The children were assessed with the Kiddie—Schedule for Affective Disorders and Schizophrenia for School Age Children—Epidemiological Version (K-SADS-E; Orvaschel and Puig-Antich, 1987), a semistructured diagnostic interview for children and adolescents aged 6–17, covering current and lifetime psychopathology. The standard procedure was to first interview the mother about the psychiatric status of the child. During the subsequent interview of the child, the interviewer attempts to resolve any discrepancies between parent and child in case of disagreement. A summary score is obtained based on positive ratings of either informant. The diagnoses are

finalized according to the best estimate procedure (Kosten and Rounsaville, 1992) at a consensus conference chaired by a psychiatrist. The girls' lifetime DSM-III-R diagnosis of a drug use disorder (abuse/dependence) related to an illicit substance (DUD) was the target outcome variable.

2.2.2. Family addiction load.
Because there is no reason to believe that the paternal DUD diagnosis (the ascertainment criterion) would account for the entirety of potential parental effects on the daughters' DUD liability phenotype (in fact, from data on alcoholism, it is maternal contribution that might have a greater effect for daughters (Bohman et al., 1981)), and to keep the analytic approach consistent with prior research on boys (Kirillova et al., 2001, 2008), we constructed a measure of parental DUD load as the sum of parental diagnoses, varying from 0 to 2 (the number of affected parents, NAP). This measure was used to analyze the relationship between parental DUD and phenotypic development (sexual maturation; the rate of disorder development) in offspring. In 54.5% of the couples none of the parents had a DUD (NAP = 0), in 29.5% one parent was affected (NAP = 1), and in 15.9% both parents were affected (NAP = 2).

2.2.3. Sexual maturation.
Sexual maturation in girls was assessed at visits 1–3 by a trained registered nurse using Tanner staging (TS; Marshall and Tanner, 1970), based on pubic hair development. To remove the confounding effect of age at a visit as a source of covariation between variables at that assessment, it was regressed out of the visit-specific Tanner stage (the residuals from regression on age at a visit were used in the analysis).

2.2.4. Nutritional status (adiposity).
Nutritional status (NS) was evaluated by the caliper subscapular skinfold (SSF) measurement as well as by the body mass index (BMI). The measurements were taken by a trained registered nurse. The mean of three SSF measurements was recorded. The skewed distributions of SSF measurements were log-transformed for analysis. The study focused on the dimensional measure of nutritional status rather than the diagnosis of obesity. The diagnosis is based on an arbitrary threshold and, statistically, may result in information loss. Therefore, for analyses, we did not dichotomize the BMI distribution by the obesity categorization. In this sample, according to the sex- and age-specific BMI thresholds of 24.6, 26.9 and 29.0 (CDC, 2001), the proportions of girls who qualified as obese were 13.8%, 19.8%, and 16.9% at the three visits, respectively. These frequencies are consistent with age-specific populational estimates (Ogden et al., 2012).

2.2.5. Peer deviance.
Peer deviance (PD) was evaluated at visits 1–3 using the Peer Delinquency Scale (Loeber, 1989), a Likert-type instrument reflecting the child's assessment of her friends' involvement in activities of various severity, from skipping school to armed robbery. The skewed score distribution was log-transformed for analysis.

2.3. Statistical analysis

Correlation, logistic regression, and survival (Cox proportional hazard regression) analyses were used to evaluate the relationships between parental DUD, nutritional status, sexual maturation, peer delinquency, and the daughter's lifetime DUD diagnosis. Path analysis was then performed to test the overall model. Analyses were conducted using SPSS and Amos software for Windows (Version 21), and G*Power 3.1 (Faul et al., 2009). Bayesian structural equation modeling (SEM) implemented in Amos was used for path analysis with the binary dependent variable of the DUD diagnosis. Bayesian estimation method has been shown to be more robust than the maximum likelihood approach in parameter estimation