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Familial Transmission of Derived Phenotypes for Molecular Genetic Studies of Substance Use Disorders

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Abstract

Although family, twin, and adoption studies indicate that genes play a significant etiologic role in the development of substance use disorders (SUDs), detecting specific genes has been difficult due to uncertainties about how to define SUDs, genetic heterogeneity and variable phenotypic expression of SUD genotypes. We used data from families recruited into six contemporaneous studies of children and adults to derive candidate SUD phenotypes using principle factors factor analysis with varimax rotation. We previously found evidence of two SUD phenotypes in offspring: a psychopathology dimension and a cognitive impairment dimension. We found evidence for one SUD-related phenotype in adults that we term Psychopathology and Cognitive Impairment. Parental factor scores significantly predicted both offspring phenotypes, as well as parental SUD (OR=1.41, $p<0.001$) and offspring SUD (mother's phenotype: OR=1.34, $p=0.04$; father's phenotype: OR=1.33, $p=0.01$). Offspring phenotype predicted offspring SUD (psychopathology phenotype: OR=2.96, $p<0.001$; cognitive impairment: OR=1.33, $p=0.04$); in offspring, baseline psychopathology predicted SUD at follow-up assessments (OR=1.55, $p=0.01$). Results suggest that these candidate SUD phenotypes may be useful for genetic studies of SUD.

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Timothy E. Wilens participated in study design and execution and provided clinical comments on the manuscript.

Michael C. Monuteaux assisted with the statistical analysis. Participated in study design and execution and provided clinical comments on the manuscript.

Joseph Biederman participated in study design and execution and provided clinical comments on the manuscript.

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Keywords

Factor analysis; substance use disorders; genetic studies

1.0 Introduction

Family, twin, and adoption studies indicate that genes play a significant etiologic role in the development of substance use disorders (SUDs) (Cloninger, 1987, Luthar and Rounsaville, 1993, Merikangas, et al., 1985, 1998, Mirin, et al., 1986, Pickens, et al., 1991, Rounsaville, et al., 1991, Tsuang, et al., 1998). Although these studies have led to the widely accepted conclusion that much of the familial transmission of SUDs is due to genes, the specific genes involved have been difficult to detect. Major obstacles to identifying genes for SUDs are the lingering uncertainties about how best to define SUDs, the possibility of genetic heterogeneity and the variable phenotypic expression of SUD genotypes.

Moreover, since it is likely that multiple genes, each of small effect, combine to cause SUDs, they may not be detectable without reducing measurement error and creating measures that more directly assess the genotype and its consequences (Faraone, et al., 1995, Tsuang, et al., 1993). Furthermore, it seems unlikely that there will be a one-to-one correspondence between genetically influenced processes in the brain and the clinical phenomena that define diagnostic categories. Molecular genetic studies may thus be more fruitful if they focus on alternative phenotypes explicitly developed to maximize the power to detect genes.

Given the extensive comorbidity between SUDs and many psychiatric disorders such as depression (Tsuang, et al., 2001), anxiety (Mills, et al., 2006), bipolar disorder (Lin, et al., 2006) and attention deficit hyperactivity disorder (ADHD) (McGough, et al., 2005), it is intriguing to speculate that, when SUDs occur in the presence of psychopathology, that psychopathology may reflect the genetic susceptibility to SUDs. This idea is consistent with two bodies of evidence. First, many forms of substance use have been shown through twin and family studies to share genetic risk factors with several forms of psychopathology (Compton, et al., 2005, Kendler, et al., 2003). Second, two twin studies have shown that, although individual SUDs may have some unique sources of genetic etiology, much of the genetic susceptibility to SUDs can be explained by a common genetic diathesis (Kendler, et al., 2003, Tsuang, et al., 1998). Taken together, these findings suggest that the genetic predisposition to SUDs may be indexed by clinical features external to the diagnosis of SUDs, which are typically associated with psychopathology such as symptoms and evidence of adaptive and cognitive impairments.

To this end, the main goal of the present work was to determine if phenotypes external to the diagnosis of SUD such as psychopathology and cognitive functioning would show evidence of utility as phenotypes for genetic studies of SUD. In the first phase of this work we used a factor analysis of multiple measures collected from our large family-study program to define two phenotypes associated with SUDs in children (Faraone, et al., 2007). The results of the factor analysis suggested that the clinical features in our sample were best summarized by two factors; one indexed by psychopathology and psychosocial impairment; the other indexed by school problems and cognitive impairment. Based on correlations among siblings, the upper limits of their heritabilities were 0.46 and 0.78, respectively. Both factor scores were significantly predicted by parental SUDs. The factor with the lower heritability and stability (psychopathology and psychosocial impairment) showed weaker evidence of an association with parental SUD.

The present work sought to extend this line of research by using factor analysis to define similar phenotypes among the parental generation of the children examined in our prior study. We hypothesized we would find factors for parents that were dimensionally similar to those we found in offspring, that parent factor scores would predict offspring factor scores, and that parental factor scores would predict parental SUD as well as offspring SUD.

2.0 Methods

We used data from families recruited into six contemporaneous studies of four psychiatric conditions in children and adults: ADHD (Faraone, et al., 2000a, 2000b, 2001), panic disorder (PD) and depression (MD) (Biederman, et al., 2001a, Rosenbaum, et al., 1991), and bipolar disorder (BPD) (Wozniak, et al., 2002). These six studies had identical or near-identical designs with uniform assessment and measurement procedures. Also, the methods for data coding, entry, storage, retrieval and cleaning have been standardized and implemented across all studies. The Institutional Review Board at the Massachusetts General Hospital approved each of these studies; we obtained informed consent from adults for their assessments and assessments of their minor children. We also obtained assent from minor children.

2.1 Subjects

Probands in all studies were recruited through clinic referrals (cases) and newspaper advertisements throughout the Greater Boston area (cases and controls). We excluded potential probands if they had major sensorimotor handicaps (paralysis, deafness, blindness), current psychosis, autism, inadequate command of the English language, or a Full Scale IQ less than 80.

Three different ascertainment schemes provided ADHD families: families were recruited on the basis of (1) a Caucasian male case (ADHD) or control (non-ADHD) proband child aged 6-17 years at time of ascertainment; (2) a female case or control proband child also aged 6-17 years at time of ascertainment, without any racial or ethnic exclusions; (3) a male or female case or control proband aged 18 to 55, without any racial or ethnic exclusions. Potential probands were excluded from (1) and (2) if they had been adopted, or if their nuclear family was not available for study.

In our studies of PD and MD, we ascertained families on the basis of parent probands between 24 and 52 years old for a study of behavioral inhibition in their offspring. Parent probands included (1) adults treated for PD, (2) adults treated for MD with no history of PD or agoraphobia, and (3) adults with no anxiety or mood disorders. All adult probands had at least one child between the ages of 2 and 6 years. Only parents who received a positive lifetime diagnosis of PD or MD by psychiatric interview and had received treatment were included as cases. Comparison parents (3) were recruited through a three-stage process similar to that used in ADHD studies: potential parents were given a phone interview and if they did not endorse PD or MD, they received a structured interview; parents who did not endorse PD or MD at either assessment were included as comparison subjects.

2.1.3 BPD Studies—Two studies of BPD provided subjects for the current analysis (1) a family genetic case-control study of BPD and non-mood-disordered youth (aged 11-18) and (2) a family study of BPD youth. No ethnic, racial or gender groups were excluded from either study and (1) excluded adopted children and children whose nuclear families were unavailable. All case probands met DSM-IV criteria for lifetime BPD, and most were symptomatic at the time of the study. Control subjects in (1) were screened by a three-stage process similar to that used in ADHD child studies; potential subjects with no DSM-IV mood disorders at either assessment were selected as controls; controls in (1) were ascertained for having no mood

disorders, to decrease misdiagnosis of BPD due to “manic switching” from dysthymia or depression to BPD (Geller, et al., 1997, 2001, Strober and Carlson, 1982).

2.2 Assessments

Children received the K-SADS-E (Epidemiologic Version), a semi-structured psychiatric diagnostic interview, with established psychometric properties (Orvaschel and Puig-Antich, 1987). Diagnoses for children 17 and under were made through indirect interviews with the subject’s mother. In addition, children 12 and older were directly evaluated. To assess dimensions of psychopathology in children, we used the Child Behavior Checklist (CBCL), a standardized assessment of behavior problems and social competence of children aged 6 to 18 years, as reported by their parents or parent-surrogates. The CBCL includes the following clinical scales: Anxious/Depressed, Somatic Complaints, Withdrawn, Attention Problems, Social Interaction Problems, Thought Problems, Delinquent Behavior, and Aggressive Behavior. Eighty-five probands and siblings in the two studies of bipolar disorder received the 2001 edition of the Achenbach CBCL, while the remainder of child subjects (N=1,787) were rated using the 1991 edition. Subjects aged 18 and older received psychiatric diagnoses in the Structured Clinical Interview for DSM-IV (SCID; (Spitzer, et al., 1990)) supplemented with modules from the K-SADS-E to assess childhood diagnoses. When asking questions about disorders in the Adult ADHD study, interviewers first queried subjects about childhood symptoms, and if symptoms were present, interviewers asked about continuation of these symptoms into adulthood and the emergence of other symptoms.

Final diagnostic assignment was made after blind review of all available information by a committee chaired by Dr. Biederman and composed of three board-certified child and adolescent psychiatrists and licensed clinical psychologists. The interviewers were instructed to take extensive notes about the symptoms for each disorder. These notes and the structured interview data were reviewed by the diagnostic committee so that the Committee can make a Best Estimate diagnosis as described by Leckman et al. (1982). Definite diagnoses were assigned to subjects who meet all diagnostic criteria. Subthreshold diagnoses were assigned to those subjects who meet most, but not all, required criteria. To combine discrepant parent and offspring reports, we used the most severe diagnosis from either source as the consensus diagnosis, unless the diagnosticians suspect that the source was not supplying reliable information.

The Social Adjustment Inventory for Children and Adolescents (SAICA) (John, et al., 1987) is a semi-structured interview administered to the child or parent that measures social functioning in children 6 to 18 years old. Content areas assessed include activities, peer relations, family relations, and academic performance. A global rating score for each subscale is assigned by the rater based on individual item scores. A total score is then calculated as the arithmetic mean of all global rating scores.

We administered the Block Design, Vocabulary, Digit Span, Arithmetic, and Coding subtests of the Wechsler Intelligence Scale for Children-3rd Edition (WISC-III) (Wechsler, 1991) to children and these same subtests of the Wechsler Adult Intelligence Scale for adults (Wechsler, 1981). We also administered the reading and arithmetic subtests of the Wide Range Achievement Test- Revised (WRAT-R) (Jastak and Jastak, 1993). These tests permit estimation of Verbal, Performance, Freedom From Distractibility, and Overall IQ along with achievement scores in reading and arithmetic. Also, by examining discrepancies between IQ and achievement measures, we created an index of learning difficulties (Reynolds, 1984).

Next, we selected tests thought to reflect basic deficits in executive function. These are tasks that enabled us to study developmental processes in planning, organization, retrieval of complex visual-spatial material (Rey-Osterrieth Complex Figure), (Rey, 1944), sustained

auditory attention (auditory continuous performance test), (Beck, et al., 1956), susceptibility to interference (Stroop test) (Stroop, 1935), abstract reasoning and shift of set (Wisconsin Card Sorting Test) (Heaton, et al., 1993) and verbal learning and memory (Wide Range Verbal Learning Test for Children) (Jastak and Jastak, 1993).

All interviewers had a Master's or Bachelor's degree in a mental health field and underwent a rigorous training program lasting three to four months. Training included mastery of the instruments, learning about DSM-III-R and DSM-IV criteria, watching training tapes, observing interviews performed by experienced raters, and rating subjects under the supervision of the project coordinator. Throughout the study, the interviewers were supervised by board certified child and adolescent psychiatrists and licensed clinical psychologists. This supervision included weekly meetings and additional consultations as needed. Before doing study interviews, interviewers achieved high levels of interrater reliability with clinicians. During the study, all interviews were audiotaped for random quality control assessments by the senior staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98. Kappa coefficients for individual diagnoses included: ADHD (0.88), CD (1.0), ODD (.90), ASPD (.80), major depression (1.0), BPD (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (.95), OCD (1.0), GAD (0.95), specific phobia (0.95), PTSD (1.0) social phobia (1.0), substance use disorder (1.0), and tics/Tourette's (0.89).

We characterized the family environment with a binary measure of marital intactness (divorced/separated or intact), the five-point Hollingshead-Redlich Socioeconomic Status (SES) scale (Hollingshead, 1975) and the mean of the cohesion, conflict and expressiveness scores from the Moos Family environment scale (FES) (Moos and Moos, 1974).

2.3 Statistical Analysis

For all tests using multiple members of a single family, we used Huber-White robust estimators of variance to account for correlated data within families. We used logistic regression for binary outcomes (sex, intactness) and linear regression for quantitative outcomes (age, SES) in Table 1. We assessed risk of substance use in parents and offspring with logistic regression of a binary substance use diagnosis (any full diagnosis of alcohol or drug abuse or dependence) on case-control status.

We use principal factors factor analysis with varimax rotation to reduce the set of candidate SUD phenotypes to a smaller set of factors that capture most of the variance in our measured variables. Missing values were imputed using those variables that load on the same factor as the variable being imputed after an initial factor calculation over subjects with complete data. We limited this initial calculation to ten principal factors. After re-calculating the factors with imputed data, we chose the leading factor based on eigenvalues greater than one. We derived factor scores from this factor.

To analyze correlations between parent and child phenotypes, we used two offspring phenotypes from a prior analysis (Faraone, et al., 2007) that reflect impairment in two domains: Psychopathology and Psychosocial Impairment and School Problems and Cognitive Impairment. We calculated parent-offspring correlations from each parent's phenotype to all offspring using GEE with exchangeable correlation, identity link and Gaussian distribution; the offspring factor entered as the dependent variable in each GEE. We report the leading regression coefficient (β_1) from the GEE as our measure of correlation. We report models including a single parent as well as both parents as independent predictors. We also assessed the contribution of a subject's phenotype to SUD by using SUD diagnosis as the dependent variable in a GEE with logit link, binomial error and exchangeable correlation, with factor scores as the independent variable along with appropriate covariates. We used this procedure

to model offspring SUD dependent on parent phenotype, offspring SUD dependent on offspring phenotype and parent SUD dependent on parent phenotype.

All statistical calculations were performed in Stata 9.2 (Stata Corporation, 2005).

3.0 Results

Table 1 shows the demographic characteristics of subjects in the analysis. We included 2,743 parents who had complete data SUD data and 1,868 offspring with factor scores from our previous analysis. We used data from 1,049 parents from Control families, as determined by proband ascertainment. Similarly, we used data from 1,694 parents of Case families as determined by proband ascertainment. We found a significant effect of SUD status on sex in parents of control families, case families, and all families considered together; SUD parents were more likely to be male. We also found a significant effect of SUD on age within parents from case families and in all parents considered together; SUD parents were younger, by only one year on average. All subsequent parent analyses were corrected for age and sex of parents.

We used data from 706 offspring from Control families as determined by proband ascertainment. We also used data from 1,162 children from Case families as determined by proband ascertainment. Overall, we found a marginally significant effect of SUD on sex at the 0.1 level, with SUD offspring more likely to be male. We found SUD offspring were more likely to be male within control, case and all families. We did not find differences in SES between SUD offspring and No SUD offspring in any grouping. We found a significant effect of SUD on family intactness in offspring from Case families; however, we did not find differences in intactness between SUD and No SUD for Control families or all families. We corrected for age and sex in all models predicting offspring SUD (Tables 5 and 6).

Table 2 shows the overall risk of SUD in parents and offspring by case status. We found a significant effect of caseness on SUD in parents and offspring when we combined all studies: subjects from Case families were consistently more likely to be diagnosed with SUD than subjects from Control families. We also examined risk of SUD by ascertainment study: when we considered each set of studies separately, we found a significant effect of caseness in parents, and no differences between cases and controls in offspring.

3.1 Non-SUD Candidate Phenotypes

Table 3 presents the results of the factor analysis of Non-SUD features of parents. One factor emerged with an eigenvalue greater than one, which we called Psychosocial and Cognitive Impairment. We derived scores from this factor so that higher scores indicated greater impairment.

Table 4 shows the correlation of parent and child factor scores within families. Psychosocial and Cognitive Impairment of mothers and fathers predicted Psychopathology and Psychosocial Impairment in their offspring. The regression coefficient of maternal Psychosocial and Cognitive Impairment lost significance when we included both parents' factor scores as independent variables, although the coefficient of paternal impairment remained significant (mothers: $\beta_1=0.05$, $p=0.06$; fathers: $\beta_2=0.093$, $p=0.001$). Psychosocial and Cognitive Impairment of mothers and fathers significantly correlated with School Problems and Cognitive Impairment of their offspring. Both maternal and paternal regression coefficients remained significant in a model including both parents' scores as independent variables (mothers: $\beta_1=0.25$, $p<0.001$; fathers: $\beta_2=0.25$, $p<0.001$).

3.2 Parent and Offspring Substance Abuse

Table 5 shows the results of GEE analysis of subject SUD predicted by subject factor scores. For both parents and children, we found that higher impairment on each factor score predicted increased prevalence of SUD. The result for School Problems and Cognitive Impairment lost significance when we included case-control status as a covariate. All other results remained significant when we corrected for case-control status. Table 6 shows the results of GEE analysis of offspring SUD predicted by parental impairment. Offspring diagnosed with SUD had fathers with higher Psychosocial and Cognitive Impairment; maternal factor score did predict offspring SUD, although differences in maternal factor scores were very small. Both maternal and paternal factor scores failed to predict offspring SUD when included in the same model. In an alternative approach, we used maximum level of impairment for any parent in a family to predict any occurrence of substance abuse within offspring in a family. Parental impairment failed to predict offspring SUD in a logistic regression model controlling for age and sex of offspring (OR=1.20, 95% CI [0.87 1.66], $p=0.3$).

We also tested the hypothesis that the child factor analytic phenotypes measured at baseline would predict SUD at the follow-up assessment. For our two ADHD studies with at least one completed follow-up, ten percent of subjects (85 of 848 subjects from the above analyses with follow-up data) developed a SUD by follow-up. The child's baseline Psychopathology and Psychosocial Impairment score (assessed at a mean age of 11.1 ± 3.1) was a significant predictor of SUD (assessed at a mean age of 14.0 ± 3.9) controlling for sex and follow-up age (OR=1.55, 95% CI=[1.27 2.42], $p=0.01$); this result maintained significance when we included case-control status as a covariate. Baseline School Problems and Cognitive Impairment did not predict follow-up SUD (OR=1.25, 95% CI=[1.00 1.61], $p=0.08$).

4.0 Discussion

From the first phase of this research we know that the non-SUD clinical features of the children were best summarized by two factors; one indexed by psychopathology and psychosocial impairment; the other indexed by school problems and cognitive impairment (Faraone, et al., 2007). These child factor scores both showed evidence of longitudinal stability, heritability and association with parental SUDs. The present study extends these prior results by showing that the single factor derived from our data on parents was associated with parental SUD and with each of the two factors we previously derived on the offspring. We also found that the child's baseline Psychopathology and Psychosocial Impairment score was a significant predictor of the onset of SUD within a 3-year follow-up period. These data provide additional support for the idea that candidate SUD phenotypes such as psychopathology and cognitive functioning, which are external to the diagnostic criteria for SUDs, may be useful for genetic studies of SUD. For example, having a quantitative trait that is associated with the genetic vulnerability to SUDs may improve power by increasing the number of informative families and subjects and by allowing for the selection of extremely ill or extremely well individuals.

From a family study, we cannot determine if familial associations between parent and child factor scores is due to genes or to shared environmental risk factors, or some combination of the two. Nonetheless, our finding is consistent with twin data suggesting that most drug use disorders share a common genetic diathesis (Kendler, et al., 2003, Tsuang, et al., 1998). If that is true, it seems reasonable to posit that members of SUD families share an underlying trait that may be indexed by psychopathological or associated cognitive features.

In contrast to our child data, which were best summarized by two factors (one indexed by psychopathology and psychosocial impairment; the other indexed by school problems and cognitive impairment) the parent data were best summarized by a single factor indexed by psychopathology and psychosocial impairment. The reason for these differences in factor

scores is unclear. One simple explanation is that among parents the school problem variables were assessed retrospectively by self report. In contrast, for children, school problems were assessed by parental report based on school behavior more proximal to the time of the interview. More work, however, will be needed to further examine this issue

The two factors extracted from our previous analyses appear to represent general cognitive ability and general psychopathology rather than specific components of either cognition or specific comorbid conditions. This finding is consistent with prior literatures in both areas. Since the time of Spearman, many researchers have posited that cognition is comprised of a general intelligence (g factor) that serves as a foundation for specific strengths and weaknesses in areas such as memory and attention. Gottfredson (2004) presents evidence that g is a strong predictor of health outcomes, including cigarette, alcohol and substance use, as well as accidents related to use.

Although categorical systems such as DSM-IV tend to emphasize differences among disorders, dimensional approaches to psychopathology have suggested that one or more general psychopathology factors may exist (Helzer, et al., 2006). A good example is the Child Behavior Checklist (CBCL), which includes broadband internalizing and externalizing scales as well as narrower clinical scales assessing specific components of psychopathology. Biederman et al (2001b) showed stability of CBCL scales within ADHD individuals over time, providing potential axes of general psychopathology. McGue et al (2006) found evidence of an underlying psychopathology dimension predicting both alcohol abuse in adolescence and general externalizing psychopathology in adulthood. Our finding of general factors (external to SUD) suggests that, if these factors prove useful for the detection of substance use disorder genes, they are likely to detect genes that are shared across substances of abuse and shared with psychopathological conditions.

When incorporated into genetic studies of substance use or ADHD, our candidate SUD phenotypes may have the potential to afford enhanced statistical power for the detection of genes. Outside the context of substance use, there is ample evidence that our non-SUD candidate phenotypes are at least partially genetically mediated. For instance, a substantial genetic component has been well established for most psychiatric disorders (Faraone, et al., 1999, NIMH, 1997, Tsuang and Tohen, 2002) and for cognitive ability (Bouchard, et al., 1990, Plomin and Craig, 2001). Other researchers attempting to apply our results to their samples will face some obstacles. Since it is unlikely that our exact factor score coefficients will generalize to all samples, re-estimating coefficients for other samples (if large enough) would seem reasonable.

Our results also have implications for the development of new diagnostic classifications. Current classification systems rely on categorical approaches to psychopathology, which is understandable given the need for clinicians to make categorical decisions. Nonetheless, as this work suggest, dimensional approaches to drug abuse also have value and should be considered in the diagnostic nosology. Our data also stress the value of impairment measures as providing useful data. As discussed by Gordon et al, although impairment is frequently required in diagnostic criteria, it is rarely operationalized with any precision. And, although it would be premature to include genetic data as diagnostic criteria, one can foresee a future in which the subject's genotype become an integral part of a substance abuse diagnosis.

Our study should be interpreted within the context of several limitations. Because our probands were clinically referred, our results may not generalize to population samples. In addition, this is a secondary analysis of several data sets, each of which had been collected to test other primary hypotheses. Although all these studies were conducted at the same research center

using the same methodology, it is possible that between study differences might be accounted for by some unmeasured factor that differed in the study implementations.

Despite these limitations, our work suggests that phenotypes external to the diagnostic criteria for SUDs are heritable, moderately stable and show a familial association with SUDs. This suggests that these phenotypes, particularly the measure of school problems and cognitive impairments, will be useful for molecular genetic studies.

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Table 2

Risk of substance abuse in parents and offspring

	Parents					Offspring				
	Control Families N=1,049	Case Families N=1,694	OR	95% CI	p	Control Families N=706	Case Families N=1,162	OR	95% CI	p
All subjects ¹	385(37)	914(54)	2.02	[1.70 2.40]	<0.001	21(3)	73(6)	2.19	[1.29 3.71]	0.004
By Ascertainment ²										
ADHD Studies	273(36) N=765	512(51) N=995	1.91	[1.55 2.35]	<0.001	13(3) N=468	29(5) N=618	1.72	[0.88 3.37]	0.11
Panic/Depression Study	34(36) N=117	199(59) N=339	2.53	[1.83 4.36]	<0.001	0(0) N=99	1(0.5) N=209	--	--	1.0 ³
Bipolar Studies	70(42) N=167	203(56) N=360	1.75	[1.14 2.70]	0.01	8(6) N=139	43(13) N=335	2.4	[0.96 6.05]	0.06

¹ Frequency (%) endorsing lifetime substance or alcohol abuse; logistic regression with Huber-White robust standard error estimates over families

² Family caseness determined by proband status

³ Fisher's exact test

Table 3
Factor Analysis of Non-SUD Candidate Phenotypes in parents

Eigenvalue Rotated Factor Loadings	Factor: Psychosocial and Cognitive Impairment	
	2.1	Uniqueness
Number of Lifetime Diagnoses	-0.27	0.93
Number of School Problems	-0.48	0.77
Occupation	0.12	0.99
FES Mean	0.14	0.98
Full IQ	0.76	0.42
WRAT	0.85	0.28
Mean Standardized Neuropsychological Score	0.69	0.53

Table 4

Correlation of Parent and Child Factor Scores

	r	Standard Error ^{<i>J</i>}	95% CI	p
Psychopathology and Psychosocial Impairment				
Mother	0.09	0.03	[0.035 0.137]	0.001
Father	0.11	0.03	[0.059 0.16]	<0.001
School Problems and Cognitive Impairment				
Mother	0.37	0.03	[0.32 0.42]	<0.001
Father	0.35	0.03	[0.30 0.39]	<0.001

^{*J*} Semi-robust standard error grouping over families

Table 5
Substance use predicted by factor scores in parents and offspring¹

Parents	No SUD N=1,426	SUD N=1,269	OR	95% CI	p
Psychosocial and Cognitive Impairment Offspring	-0.11±0.90 N=1,774	0.13±0.90 N=94	1.41	[1.28 1.54]	<0.001
Psychopathology and Psychosocial Impairment School Problems and Cognitive Impairment	-0.05±0.90 -0.003±0.86	0.90±0.90 0.02±0.74	2.96 1.33	[2.22 3.93] [1.02 1.73]	<0.001 0.04

¹ GEE predicting SUD with factor score as independent variable and clustering over

² Mean±SD factor scores

Table 6
Offspring Substance Abuse Predicted by Parental Psychosocial and Cognitive Impairment Factor Score

Parent	No SUD	SUD	OR	95% CI	p
Mother	0.13±0.87 N=1,741	0.12±0.85 N=92	1.34	[1.01 1.77]	0.04
Father	-0.17±0.95 N=1,636	-0.10±0.9 N=78	1.33	[1.03 1.70]	0.01

⁴ GEE predicting offspring SUD with parent factor score as independent variable and clustering over families

⁵ Mean±SD parent factor scores