Published in final edited form as:
J Psychiatr Res. 2008 July ; 42(8): 644–652.

Externalizing Disorders in the Offspring from the San Diego Prospective Study of Alcoholism

Marc A. Schuckit, M.D, **Tom L. Smith, Ph.D**, **Juliann Pierson, M.A**, **Ryan Trim, Ph.D**, and **George P. Danko, Ph.D.**

Keywords

Children of alcoholics; Genetics; Externalizing problems

I. Introduction

Externalizing characteristics have been defined both more generally as a range of disruptive childhood behaviors, and more specifically as a combination of personality characteristics (e.g., impulsivity and sensation seeking) and physiological and cognitive attributes related to childhood behavioral problems (Hesselbrock and Hesselbrock, 1992; King et al., 2004; Porjesz et al., 1998; Sher, 1991; Tarter et al., 2003). Regardless of the definition, several psychiatric diagnoses have been subsumed under the broad umbrella of externalizing conditions in childhood, including conduct disorder (CD), i.e., early onset aggressive behavior likely to lead to later antisocial personality disorders (ASPD) (Hesselbrock and Hesselbrock, 1992; Scourfeld et al., 2004; Slutske et al., 1998; Thapar et al., 2005), and attention deficit hyperactivity disorder (ADHD), i.e., deficits in focusing attention along with signs of hyperactivity (Biederman et al., 1995; Pedersen et al., 2001). Various studies have reported a link between externalizing behaviors and family histories (FHs) of alcohol use disorders (AUDs), illicit substance use disorders (SUDs), some personality conditions such as ASPD, and mood disorders, especially manic depressive disease (Biederman et al., 1992, 2001; Henin et al., 2005; Hesselbrock and Hesselbrock, 1992; Ohannessian et al., 2004 a, b; Zucker et al., 2000). Among mood disorders, the link to bipolar illness appears to be particularly strong (Biederman et al., 2000; Henin et al., 2005; Wozniak et al., 2001). In addition, young subjects with externalizing conditions have been reported to have higher rates of aggressiveness, antisocial behaviors, substance-related disorders, and manic depressive disease (Chang et al., 2000; Egeland et al., 2003; Emsinger et al., 2002; Fridell et al., 2006; Hirshfield-Becker et al., 2006; Pedersen et al., 2001; Raine et al., 1998).

The lifetime risk for externalizing syndromes in populations varies across studies, perhaps reflecting differences in the groups evaluated, as well as the methods and definitions used. An estimated 4%-to-9% of children in the general population may have ever demonstrated CD, and between 3% and 8% ever met criteria for ADHD (Costello et al., 1996; Kessler et al., 2005; Lynskey and Hall, 2001). These diagnoses can be made during childhood, and all have a significantly higher prevalence in males than females.

Correspondence Address: Department of Psychiatry (116A), University of California, San Diego and the, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161-2002, Tel: (858) 552-8585 X7978, Fax: (858) 552-7424, e-mail: mschuckit@ucsd.edu.

ADHD sometimes co-occurs with CD (Biederman et al., 1996, 1998; Lynskey and Hall, 2001), a situation that can make it difficult to determine whether a characteristic is related to one or both of these disorders. The appearance of CD among ADHD children is associated with a more severe clinical course than might be expected with ADHD alone, including an earlier onset of more intense antisocial behaviors (Biederman et al., 1992; Thapar et al., 2001; Todd et al., 2001). While ADHD and CD share the clinical characteristics of disruptive behaviors, some electrophysiological correlates, such as the amount of fast beta power on background cortical electroencephalograms (EEGs), may be different across individuals with these diagnoses (Barry et al., 2003; Bauer and Hesselbrock, 1993). Also, although studies indicate an enhanced risk for future alcohol and drug use and problems for children with CD, there is less agreement regarding such outcomes for those with ADHD without comorbid CD (Biederman et al., 1995, 1998; Span and Earleywine, 1999), with several studies concluding that ADHD alone did not predict substance involvement (Disney et al., 1999; Fergusson et al., 1993; Halikas et al., 1990; Pedersen et al., 2001). The probability of substance use and problems for subjects with ADHD may also be higher in individuals with low cognitive performance (Span and Earleywine, 1999), and when reported from studies where the ADHD histories were gathered retrospectively from adults (Lynskey and Hall, 2001).

The risk for AUDs appears to relate to several relatively independent phenotypes (Schuckit, 2002). One such endophenotype involves impulsivity and disinhibition as expressed in CD and ASPD (Schuckit and Smith, 2006; Slutske et al., 1998), and another relates to alcohol-metabolizing enzymes (Li, 2000). The potential impact of these factors had been established by the 1970's when the current San Diego Prospective Study began, and the decision was made to focus on additional characteristics that might contribute to the AUD risk. Despite exclusion of antisocial subjects, over 40% of the original 20-year-old probands with an FH of AUDs developed alcohol abuse or dependence over the subsequent 15 years, demonstrating the importance of additional risk factors (e.g., the level of response to alcohol) to the development of alcoholism (Schuckit and Smith, 2000). The expansion to evaluation of the children of the probands from our study offers the opportunity to observe outcomes in offspring from alcoholic families while controlling for the impact of more severe impulsivity (i.e., ASPD) in parents and grandparents (Schuckit and Gold, 1988; Schuckit and Smith, 2000; Schuckit et al., 2002). When these children were an average age of about 10 years, we reported no significant relationship between externalizing disorders or symptoms and the FH of AUDs, although there was a significant correlation between the FH of mood disorders and externalizing symptoms (Schuckit et al., 2000b, 2003b). Consistent with other studies highlighting the importance to behavioral problems of the milieu in which a person lives (Biederman et al., 2002; Connolly et al., 1993; Dick et al., 2006; Rhee and Waldman, 2002), the absence of either a biological father or mother in the home of upbringing was also related to externalizing scores at this early age. However, these offspring were too young to allow us to adequately evaluate their substance use and problems.

In summary, while the literature generally supports an elevated risk for externalizing behaviors and related disorders in children from alcoholic families along with an associated enhanced risk for alcohol and drug use and problems, this may not apply to all families, and the clearest correlation is seen for CD. The role of ADHD after controlling for CD is more open to question. The current analyses report data regarding these issues from teenage and young adult offspring from the San Diego Prospective Study at an average age of 17 years. The key hypotheses are: 1) in the absence of an FH of ASPD, externalizing conditions will still correlate with the FH of AUDs and mood disorders; 2) a diagnosis of CD in these offspring will correlate positively with their substance use and problems; and 3) ADHD in the absence of CD in these higher-educated families will not be related to substance use and problems.

II. Methods

These analyses gathered data from a recent follow-up of offspring age 14 through 25 from the San Diego Prospective Study. All offspring and parents gave informed consent (and for those less than age 18, informed assent with parental consent) to participate in this ongoing protocol (Schuckit and Gold, 1988; Schuckit and Smith, 2000). Age 14 was selected as the minimum because the two externalizing conditions were likely to be apparent by that time and as an age by which almost 25% of the children will have used at least one illicit drug (40% by age 16), and 45% will have used alcohol (65% by age 16) (Johnston et al., 2005; Slutske et al., 1998). In addition, the age range for sons and daughters was also chosen to reflect an early point for which personal interviews were obtained, and the fact that the adolescent version of the standardized interview described below was used at T25 for all offspring through age 25.

The initial probands, the fathers of these offspring, had been identified between 1978 and 1988 from 18-to-25-year-old Caucasian male respondents to a questionnaire mailed to random students and nonacademic staff at the University of California San Diego. Subjects were selected regardless of their FH of additional Axis I diagnoses. The study was limited to Caucasians (including White Hispanics) because this was the major group living in San Diego and as a step to avoid the impact of race on the alcoholism risk through intense responses to alcohol (e.g., as seen in Asians) (Li, 2000). To participate, a person had to have had experience with alcohol but not be alcohol or drug dependent nor have ASPD, not have a father with ASPD, and participants were chosen so that approximately half had an alcohol-dependent father (i.e., they were FH positive), with each of these men matched to an FH negative control on demography and substance use histories. The exclusion of subjects with ASPD reflected the fact that impulsivity (extreme in that condition) is only one of several intermediate phenotypes related to the alcoholism risk, it is noted in only a minority of alcoholics, it enhances the risk for multiple severe conditions (not just AUDs), and it may not relate to additional endophenotypes such as alcohol-metabolizing enzymes or the level of response to alcohol (Schuckit, 2002;Slutske et al., 1998). At intake, the probands were evaluated for several characteristics hypothesized to be related to the later risk for alcoholism, including their experience with alcohol, nicotine and other substances, personality attributes, and their level of response to alcohol (Schuckit, 2002;Schuckit and Gold, 1988).

Follow-ups were carried out 10 years after the initial evaluation (99% completed interviews), and again at 15 years (98% complete), 20 years (approximately 95% complete), along with the current ongoing 25-year follow-up (Schuckit and Smith, 1996, 2000). As subjects married, their spouses entered the study and supplied follow-up information about the proband, along with a similar interview regarding her own background, and reporting on pregnancy or birth problems for all new children (Schuckit and Smith, 2000; Schuckit et al., 2000b). The 10-year follow-up instrument for probands and spouses was based on questions derived from the Schedule of Affective Disorders and Schizophrenia (SADS), along with changes consistent with subsequent versions of that instrument (Spitzer and Endicott, 1977; Spitzer et al., 1992). Items in the 15-year interview and beyond were expanded to cover additional information using questions taken from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview (Bucholz et al., 1994; Hesselbrock et al., 1999). Beginning with the 15-year follow-up, adult children were evaluated using an instrument similar to the proband follow-up, while younger offspring beginning at age 12 were administered the face-to-face SSAGA interviews developed for adolescents, known as the C-SSAGA-A (Barnow et al., 2002; Kuperman et al., 2001), using diagnoses from the Third Revised Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III-R) (American Psychiatric Association, 1987). The SSAGAs demonstrate good retest and across interviewer reliabilities, along with kappas for most diagnoses relevant here of 0.60 and higher (Bucholz et al., 1994). A parallel version of the SSAGA uses the mothers' reports on children and

adolescents age seven and above, the C-SSAGA-P (Kuperman et al., 2001). These multiple data sources were used to generate offspring CD and ADHD diagnoses, and the "worst case scenario" procedure advocated by Bird et al (1992) was used where a son or daughter was considered positive for a diagnoses if either the parent or offspring interview supported such a classification.

FH data regarding DSM-III-R alcohol and drug use disorders, major depressions, bipolar disorder, and other psychiatric conditions were gathered through face-to-face interviews with the original proband (the father of these offspring) and his spouse (the mothers of these subjects) every five years, each of whom gave reports about themselves and their biological parents. The latter were gathered through a format similar to that of the Family History Module (FHAM) of the SSAGA (Rice et al., 1995). Demographic information for the offspring was extracted from the offspring and parent interviews, with alcohol and drug-related items representing the highest level of involvement indicated by either parent or offspring.

Data for the major analyses compared the cross-sectional outcomes of offspring with the two externalizing conditions at either follow-up point for subjects, using t-tests for continuous variables and chi square (χ^2) for categorical data. Similar analyses compared characteristics of offspring with and without alcohol or drug use disorders. Hierarchical multiple linear logistic regression analyses were used to evaluate how the combination of background variables best related to the designation of these externalizing conditions and to a diagnosis of an AUD and/or SUD in these offspring. The relevant tables present odds ratios (OR's), pseudo R^2s (an estimate of the proportion of the variance explained overall), and the change in R^2 when the key item (e.g., an FH of bipolar disorder) was added as the second step in the regression. Although logistic regression is a non-parametric test evaluating likelihoods of 'group membership,' the amount of variance accounted for is most easily addressed through pseudo R^2s, and these reflect the computed likelihoods. In the context of dichotomous outcomes (e.g., the presence or absence of CD or ADHD), the logistic regression indicates the probability of being in a specific group.

III. Results

The subjects are 165 offspring from 93 families in the San Diego Prospective Study who were between the ages of 14 and 25 years, and who had personal interviews with themselves and a parent during the 20- or 25-year follow-up phases of the protocol up to June 30, 2006. About 70% of these sons and daughters were age 16 and above. The 93 families had an average of 1.8 ± 0.91 children, including 54 families with more than one child in the age range, although 81 families had only one or two offspring.

The 165 young subjects represent approximately 95% of those eligible for evaluation and who were in the selected age range by the time of the current data harvest. For these analyses, the subjects were initially placed into two mutually exclusive groups. The first consisted of the 17 individuals (10.3%) who met criteria for externalizing conditions of CD (10 subjects or 6.1% of the 165 participants) or ADHD (eight individuals - 4.8% of the total, a figure that increased to 6.1% if the two CD subjects who also had ADHD were included). It should be noted that no subject met criteria for oppositional defiant disorder in the absence of CD. In order to create mutually exclusive groups, consistent with the data indicating the antisocial and substance use patterns might relate more closely to the conduct diagnosis (Biederman et al., 1995; Disney et al., 1999; Span and Earleywine, 1999), subjects were labeled as CD if they fulfilled these criteria, and ADHD only if CD had not been noted. Broken down by sex, among the 85 males, nine (10.6%) fulfilled criteria for CD, and six (7.1%) had ADHD, a figure that increased to 9.4% if the two CD subjects with concomitant ADHD were included. For the 80 females, one

each (1.3%) met criteria for CD and for ADHD. Overall, the 165 subjects had a mean age of 17.5 (2.99) years, 52.7% were male, and 97.0% were Caucasian (including White Hispanic).

Table 1 compares demographic, FH, and psychiatric outcome-related data for the 17 offspring with externalizing conditions and the 148 who had no such diagnoses. The two groups were comparable on age, as well as the father's (i.e., the proband's) education and family income. However, the 17 offspring in Group 1 were more likely to be male, less likely to be Caucasian (i.e., Anglo-European and White Hispanic), and more likely to have had divorced parents. Regarding race, almost all the designation of non-Caucasians reflected an original White proband (father) and a racial minority mother (Black, Filipino, or other Asian). The slightly lower education for Group1 mothers related to one woman from South America who only completed the eighth grade, and the difference between groups became nonsignificant once she was excluded. Despite the fact that the groups were created based on their own externalizing syndromes, there were no significant differences between offspring in Groups 1 and 2 for their personal rates of any additional psychiatric conditions. Finally regarding Table 1, while the two groups were similar regarding the presence of at least one parent or two grandparents with alcohol or drug abuse or dependence (i.e., the shared 50% of their genes with a person with these disorders), or a major depressive episode, Group 1 subjects were more likely to have had such a FH of manic depressive (i.e., bipolar) disorder.

While not shown in the table, the diagnoses in offspring were also evaluated separately for the 56 subjects who had an alcoholic parent or two alcoholic grandparents versus the 109 FH negative individuals. Members of the two family groups were similar on proportions with CD (7.1% vs. 5.5%, $\chi^2 = .17$, p = .68) and ADHD without CD (5.4% vs. 5.5%, $\chi^2 = .002$, p = .97), as well as on the personal histories of independent major depressions (5.4% vs.1.8%, $\chi^2 = 1.56$, p = .21), bipolar disorder (1.8% vs. 0.9%, $\chi^2 = 0.23$, p = .63), anxiety disorder (5.4% vs. 2.8%, $\chi^2 = 0.72$, p = .40), and other diagnoses (0% vs.1.8%, $\chi^2 = 1.04$, p = .31).

Differences in substance use patterns for subjects are presented in Table 2. While similar proportions ever drank alcohol, drinkers in Group 1 had higher maximum drinks (a drink ~10 gm ethanol), and were more likely to have experienced alcohol problems as generated from a list of 23 items not designated as specific DSM abuse or dependence criteria, and to fulfill criteria for an alcohol diagnoses. Regarding problems, the greatest differential for Group 1 vs. Group 2 among drinkers was for blackouts (75.0% vs. 21.4%, $\chi^2 = 10.47$, p = .001), ever getting help for drinking problems (25.0% vs. 2.9%, $\chi^2 = 7.24$, p = .008), experiencing a drunk driving arrest (12.5% vs. 1.4%, $\chi^2 = 3.52$, p = .07), and alcohol-related physical fights (25.0% vs. 4.3%, $\chi^2 = 5.14$, p = .03). Offspring in Group 1 were also more likely to have ever tried drugs and to have SUDs. The figures regarding abuse and dependence reflect the entire population in each group, not just users.

Table 3 presents the results of hierarchical logistic regression using variables significantly different across groups in Table 1 to predict CD or ADHD diagnoses. Reflecting the finding regarding the FH of bipolar disorder from Table 1, and the literature potentially linking that disorder to externalizing conditions, all other items were entered as the first step and the FH entered second. The results revealed that all variables contributed, combining to explain 32.3% of the variance (the pseudo-R^2). The unique contribution of the bipolar FH (R^2 change) after considering all other relevant variables in the second step of the equation was 5.7%.

Because 54 of the families included in Tables 1 and 2 contained more than one child, steps were taken to evaluate the possible effect of non-independence on each of our two major types of outcomes, externalizing diagnoses and substance use or problems. The intraclass correlations for these outcomes were .39 and .23, and the design effects were 1.30 and 1.17, respectively. Design effects less than 2.0 indicate that multilevel modeling need not consider

non-independence as producing a notable effect (Muthén and Satorra, 1995). The lack of an impact of multiple siblings on the results presented here probably reflect the fact that 81 of the 93 families had only one or two offspring. Consistent with the absence of a major effect of non-independence, a reanalysis of results in Tables 1-to-3 after selecting one child per family (the eldest, in order to optimize the time of potential exposure to alcohol and drugs) resulted in no major changes from data reported above.

Next, the data in Tables 1 and 2 were reanalyzed separately for each of the two externalizing disorders. For the 10 offspring with CD as compared to the 148 in Group 2, despite the smaller number of subjects, all significant differences reported in Tables 1 and 2 remained similar to those shown. A repeat of the logistic regression using the predictors of CD in Table 3 for these 158 subjects revealed that 13.3% of the variance for CD was explained, with the most significant contributors parental divorce and the FH of bipolar disorder, along with a trend ($p = .06$) for male sex, but no contribution from the racial background. However when the externalizing group was limited to subjects with ADHD, most of the univariate differences in Tables 1 and 2 disappeared, except for male sex and race, and a regression predicting ADHD explained only 6.7% of the variance, with racial background the single significant contributor.

The data in Tables 1-to-3 were generated by considering an item as “endorsed” if reported by either the parent or offspring. Thus, it is relevant to note that endorsement of CD or ADHD across informants correlated at .85 ($p<.001$), while agreement for alcohol or drug diagnoses was .77 ($p<.001$). Estimates of the son or daughter’s usual quantity, frequency, and specific problems had not been asked in the parent interview.

Finally, as shown in Tables 4 and 5, an additional step was taken to clarify the optimal correlates of the development of alcohol and illicit substance-related diagnoses in the offspring. In Table 4, the 20 offspring who had alcohol and/or drug diagnoses were older, came from families with lower income, reported a higher prevalence of divorced parents, were substantially more likely to have had a diagnosis of CD but not ADHD, and were more likely to have an FH of bipolar disorder. When the items that differed significantly across groups were entered into a hierarchical logistic regression analysis with a CD diagnosis entered as the second step after considering all additional variables the equation explained 51.3% of the variance overall, with 5.7% contributed by CD, and additional contributors from an older age and lower family income.

Discussion

This paper tested three hypotheses in the offspring from well-characterized and relatively highly-educated families. The original subjects, the fathers of these offspring, had been selected to exclude very early onset alcoholism in the context of ASPD as that antisocial diagnosis is likely to be noted in 20% or less of alcohol dependent men in the general population and because it is only one of several potentially independent characteristics that impact on the alcoholism risk (Irwin et al., 1990; Schuckit, 2002; Westermeyer et al., 2005). In the current families, regarding the first hypothesis, the results did not support a prominent relationship between a FH of AUDs or SUDs and the child’s ADHD or CD, and the FH of bipolar disorders was only related to CD. These findings are consistent with results from our studies when the offspring were younger (Schuckit et al., 2000b, 2003b). Hypothesis 2 was clearly supported, as the data indicated that CD was closely related to substance use and problems, but, consistent with what was set forth in Hypothesis 3, ADHD by itself was not prominently related to substances.

The rate of CD in these offspring was 6.1%, a figure that climbed to 9.4% among males, compared to the 4%-to-9% expected in the general population (Costello et al., 1996; Kessler, 2005; Linskey and Hall, 2001). ADHD was seen in 6.1% of the offspring overall (including

two of the males in the CD group), a figure that increased to 9.4% in males, rates also close to the range of the estimated 3%-to-8% in the general population. The lack of a link in our study between the FH of alcoholism and CD or ADHD is likely to reflect the fact that alcoholism is a heterogeneous disorder, the risk for which may be related to externalizing conditions such as impulsivity in only some families. Other risk factors relatively independent of ASPD and impulsivity (e.g., alcohol-metabolizing enzymes and the level of response to alcohol) may contribute to the risk in other pedigrees (Schuckit, 2002; Schuckit, in press; Schuckit et al., 2000a). The exclusion of ASPDs from the proband group is likely to have diminished the impact of externalizing conditions on the AUD risk in these families, even though a high rate of AUDs and a rate of SUDs comparable to the general population have been documented in the San Diego Prospective Study (Schuckit and Smith, 2000; Schuckit et al., 2004). This interpretation is consistent with the conclusion that the enhanced risk for externalizing behaviors for some samples of children of alcoholics may reflect ASPD or similar disorders in these families more than the impact of the FH of alcoholism itself.

The results reported here support the contention of Bauer and Hesselbrock (1993) and others that offspring with CD may differ in some important ways from those with ADHD alone. In our analyses, only male gender predicted both of these subgroups, with the majority of the findings in Tables 1 and 2 reflecting the impact of CD. In fact, none of the ADHD offspring (in the absence of CD) had used an illicit drug, and their drinking patterns did not differ substantially from those in Group 2. These results support the contention of several additional authors that, when the impact of CD is controlled, ADHD offspring may not be at exceptionally high risk for AUDs or SUDs (Disney et al., 1999; Fergusson et al., 1993; Halikas et al., 1990).

In the current sample, once CD was observed in these offspring it had the same relationship with alcohol and drug use and problems that might be expected in any population (Slutske et al., 1998; Tarter et al., 2003; Zucker et al., 2000). Our findings expand that knowledge base by demonstrating the link can still be observed in families with higher educated and more affluent parents who do not evidence ASPD themselves. As would be expected, offspring with CD were mostly male and more likely to demonstrate both higher drinking quantities and problems, and had more pervasive patterns of use and disorders associated with substances of abuse than the 148 remaining young subjects (Egeland et al., 2003; Emsinger et al., 2002; Fridell et al., 2006). As shown in Tables 4 and 5, the relationship between CD and AUDs and/or SUDs in the sons and daughters of our probands remained robust even when considered in the context of age, income, divorced parents, and the FH of bipolar disorder.

Two background variables stand out regarding the offspring with externalizing disorders. The first is the significantly higher family rate for bipolar disorder (17.6% vs. 2.0% for the remaining 148 subjects). The potential link between externalizing conditions, especially CD, and family patterns of bipolar disorder has been noted in the literature (Biederman et al., 1999, 2000; Grigoriu-Serbanescu et al., 1989; Henin et al., 2005). The prominence of this finding in the current population is of special interest because the original probands had not been selected for any personal or FH of mood disorders. Several potential explanations for the link between bipolar FHs and externalizing conditions have been suggested, including a possible overlap in genes predisposing toward these disorders (Biederman et al., 2000; Schuckit et al., 2003a), the possibility that the concurrence of vulnerabilities to both bipolar disorder and CD may contribute to a more severe clinical course that makes such subjects easier to identify, and the suggestion that conduct-related problems may have been an alternative manifestation of the bipolar characteristics of irritability and impulsivity (Biederman et al., 2000). Regardless of the mechanisms, these findings are consistent with the projection by Henin et al. (2005) that children from bipolar families may demonstrate diverse psychiatric symptoms, including conduct and substance-related problems. However, perhaps reflecting

the relatively young age of our sample, the offspring demonstrating externalizing conditions did not have a clearly enhanced risk for any other major psychiatric conditions compared to the remaining subjects.

A second notable finding regarding background was the higher rate of divorced biological parents among the offspring with externalizing conditions. This is consistent with prior reports that family conflict and marital discord may be associated with externalizing symptoms in children (Biederman et al., 2002; Foley et al., 2004; Rutter and Quinton, 1977; Seljamo et al., 2006). However, reflecting the cross-sectional nature of our analyses, the direction of the relationship between family disruption and externalizing behaviors cannot be gauged from the current data. The symptoms might be manifestations of a reaction to a stressful situation, or might reflect consequences of potential personality characteristics that could enhance both the probability of marital dissolution and behavioral problems in the offspring.

A brief comment is required regarding the unexpected contribution in Table 3 for a minority racial background. These results do not indicate Hispanic heritage, as White Hispanics were placed together in the same category as Anglo-Caucasians. Because the minority status primarily reflects backgrounds of the mother, it is possible that some unknown aspect of parental relationships or stresses might have added to the prevalence of externalizing conditions.

The current findings must be considered in the context of the methods used. First, the number of offspring with ADHD or CD was quite small, although the rates were similar to what would be expected from the general population. This presents restrictions on statistical power that may have contributed to an inability to identify additional differences between the two groups in the tables, and several findings with p values close to significance may have become more robust if more subjects had been studied (e.g., the rate of anxiety disorders, the separate impact of alcohol abuse and dependence in Table 1, and rates of depression and FH of AUDs in Table 4). Power issues may also have been affected by non-independence, although an analysis of the design effects of non-independence did not indicate a robust impact of having multiple siblings in some families. Third, while these evaluations support the important relationships between externalizing conditions and alcohol and drug patterns and problems in these relatively affluent and more highly-educated families, it is not clear whether similar findings would be observed among families from different socioeconomic strata or racial/ethnic groups. A fourth caveat relates to the age of these offspring, as these subjects have not yet passed through the age of risk for substance related problems. In addition, it is important to remember that in our analyses the externalizing diagnoses were considered to be mutually exclusive, using a hierarchy of CD and ADHD. Thus, we were unable to evaluate the impact of comorbidity between these externalizing conditions. Finally, our evaluations were cross-sectional, and there were too few offspring with oppositional defiant disorder alone (i.e., in the absence of CD) to adequately evaluate.

Acknowledgements

This work was supported by NIAAA Grant No. 05526; the Veterans Affairs Research Service; funds provided by the State of California for Medical Research on Alcohol and Substance Abuse through the University of California San Francisco; and a grant from CompassPoint Addiction Foundation.

References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). 3 revised. Washington, DC: American Psychiatric Association; 1987.

Barnow S, Schuckit MA, Smith TL, Preuss U, Danko GP. The relationship between the family density of alcoholism and externalizing symptoms among 146 children. Alcohol and Alcoholism 2002;37:383–7. [PubMed: 12107042]

Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I Qualitative and quantitative electroencephalography. Clinical Neurophysiology 2003;114:171–83. [PubMed: 12559224]

Bauer LO, Hesselbrock VM. EEG, autonomic and subjective correlates of the risk for alcoholism. Journal of Studies on Alcohol 1993;54:577–89. [PubMed: 8412148]

Biederman J, Faraone SV, Chu MP, Wozniak J. Further evidence of a bidirectional overlap between juvenile mania and conduct disorder in children. Journal of the American Academy of Child and Adolescent Psychiatry 1999;38:468–76. [PubMed: 10199120]

Biederman J, Faraone SV, Hirshfeld-Becker DR, Friedman D, Robin JA, Rosenbaum JF. Patterns of psychopathology and dysfunction in high-risk children of parents with panic disorder and major depression. American Journal of Psychiatry 2001;158:49–57. [PubMed: 11136633]

Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, et al. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder: Patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. Archives of General Psychiatry 1992;49:728–38. [PubMed: 1514878]

Biederman J, Faraone S, Milberger S, Guite J, Mick E, Chen L, et al. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. Archives of General Psychiatry 1996;53:437–46. [PubMed: 8624187]

Biederman J, Faraone SV, Monuteaux MC. Differential effect of environmental adversity by gender: Rutter's index of adversity in a group of boys and girls with and without ADHD. American Journal of Psychiatry 2002;158:1556–62. [PubMed: 12202277]

Biederman J, Faraone SV, Wozniak J, Monuteaux MC. Parsing the association between bipolar, conduct, and substance use disorders: A familial risk analysis. Biological Psychiatry 2000;48:1037–44. [PubMed: 11094136]

Biederman J, Wilens TE, Mick E, Faraone SV, Spencer T. Does attention-deficit hyperactivity disorder impact the developmental course of drug and alcohol abuse and dependence? Biological Psychiatry 1998;44:269–73. [PubMed: 9715358]

Biederman J, Wilens T, Mick E, Milberger S, Spencer TJ, Faraone SV. Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): Effects of ADHD and psychiatric comorbidity. American Journal of Psychiatry 1995;152:1652–8. [PubMed: 7485630]

Bird HR, Gould MS, Staghezza B. Aggregating data from multiple informants in chid psychiatry epidemiological research. Journal of the American Academy of Child and Adolescent Psychiatry 1992;31:78–85. [PubMed: 1537785]

Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI Jr, et al. A new semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. Journal of Studies on Alcohol 1994;55:149–58. [PubMed: 8189735]

Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. Journal of the American Academy of Child and Adolescent Psychiatry 2000;39:453–60. [PubMed: 10761347]

Connolly GM, Cassell S, Stewart J, Silva PA, O'Brien MK. The effect of parents' alcohol problems on children's behaviour as reported by parents and by teachers. Addiction 1993;88:1383–90. [PubMed: 8251876]

Costello EJ, Angold A, Burns BJ, Erkanli A, Stangl DK, Tweed DL. The Great Smoky Mountains study of youth. Archives of General Psychiatry 1996;53:1137–43. [PubMed: 8956680]

Dick DM, Agrawal A, Schuckit MA, Bierut L, Hinrichs A, Fox L, et al. Marital status, alcohol dependence, and *GABRA2*: Evidence for gene-environment correlation and interaction. Journal of Studies on Alcohol 2006;67:185–94. [PubMed: 16562401]

Disney ER, Elkins IJ, McGue M, Iacono WG. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. American Journal of Psychiatry 1999;156:1515–21. [PubMed: 10518160]

Egeland J, Shaw J, Endicott J, Pauls D, Allen C, Hostetter A, et al. Prospective study of prodromal features for bipolarity in well Amish children. Journal of the American Academy of Child and Adolescent Psychiatry 2003;42:786–96. [PubMed: 12819438]

Emsinger ME, Joon HS, Fothergill KE. Childhood and adolescent antecedents of substance use in adulthood. Addiction 2002;97:833–44. [PubMed: 12133122]

Fergusson DM, Lynskey MT, Horwood L. Conduct problems and attention deficit behaviour in middle childhood and cannabis use by age 15. The Australian and New Zealand Journal of Psychiatry 1993;27:673–82. [PubMed: 8135692]

Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J, et al. Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. Archives of General Psychiatry 2004;61:738–44. [PubMed: 15237086]

Fridell M, Hesse M, Johnston E. High prognostic specificity of antisocial personality disorder in patients with drug dependence: Results from a five-year follow-up. American Journal on Addictions 2006;15:227–32. [PubMed: 16923669]

Grigoroiu-Serbanescu M, Christodorescu D, Jipescu I, Totoescu A, Marinescu E, Ardelean V. Psychopathology in children aged 10–17 of bipolar parents: psychopathology rate and correlates of the severity of the psychopathology. Journal of Affective Disorders 1989;16:167–79. [PubMed: 2522116]

Halikas JA, Meller J, Morse C, Lyttle MD. Predicting substance abuse in juvenile offenders: attention deficit disorder vs aggressivity. Child Psychiatry and Human Development 1990;21:49–55. [PubMed: 2397654]

Henin A, Biederman J, Mick E, Sachs GS, Hirshfeld-Becker DR, Siegel RS. Psychopathology in the offspring of parents with bipolar disorder: A controlled study. Biological Psychiatry 2005;58:554–61. [PubMed: 16112654]

Hesselbrock M, Hesselbrock VM. Relationship of family history, antisocial personality disorder and personality traits in young men at risk for alcoholism. Journal of Studies on Alcohol 1992;53:619–25. [PubMed: 1434635]

Hesselbrock M, Easton C, Bucholz KK, Schuckit M, Hesselbrock V. A validity study of the SSAGA—a comparison with the SCAN. Addiction 1999;94:1361–70. [PubMed: 10615721]

Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Cayton GA, Rosenbaum JF. Laboratory-observed behavioral disinhibition in the young offspring of parents with bipolar disorder: A high-risk pilot study. American Journal of Psychiatry 2006;163:265–71. [PubMed: 16449480]

Irwin M, Schuckit MA, Smith TL. Clinical importance of age at onset in Type 1 and Type 2 primary alcoholics. Archives of General Psychiatry 1990;47:320–24. [PubMed: 2322083]

Johnston, LD.; O'Malley, PM.; Bachman, JR.; Schulenberg, JE. Monitoring the future: National Survey Results on Drug Use, 1975-2004: Vol. 1, Secondary school students. NIH Publication No. 05-5727. Bethesda, MD: National Institute on Drug Abuse; 2005.

Kessler RC, Berglund P, Demler O, Jin R, Walters MS. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication. Archives of General Psychiatry 2005;62:593–602. [PubMed: 15939837]

King SM, Iacono WG, McGue M. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. Addiction 2004;99:1548–59. [PubMed: 15585046]

Kuperman S, Schlosser SS, Kramer JR, Bucholz K, Hesselbrock V, Reich T, et al. Risk domains associated with an adolescent alcohol dependence diagnosis. Addiction 2001;96:629–36. [PubMed: 11300966]

Li T-K. Pharmacogenetics of responses to alcohol and genes that influence alcohol drinking. Journal of Studies on Alcohol 2000;61:5–12. [PubMed: 10627090]

Lynskey MT, Hall W. Attention deficit hyperactivity disorder and substance use disorders: is there a causal link? Addiction 2001;96:815–22. [PubMed: 11399213]

Muthén, B.; Satorra, A. Complex sample data in structural equation modeling. In: Marsen, P., editor. Sociological Methodology. 1995. p. 216-316.

Ohannessian CM, Hesselbrock VM, Kramer J, Kuperman S, Bucholz KK, Schuckit MA, et al. The relationship between parental alcoholism and adolescent psychopathology: A systematic examination of parental comorbid psychopathology. Journal of Abnormal Child Psychology 2004a; 32:519–33. [PubMed: 15500031]

Ohannessian CM, Hesselbrock VM, Kramer J, Bucholz KK, Schuckit MA, Kuperman S, et al. Parental substance use consequences and adolescent psychopathology. Journal of Studies on Alcohol 2004b; 65:725–30. [PubMed: 15700509]

Pedersen W, Mastekaasa A, Wichstrom. Conduct problems and early cannabis initiation: a longitudinal study of gender differences. Addiction 2001;96:415–31. [PubMed: 11255582]

Porjesz B, Begleiter H, Reich T, Van Eerdewegh P, Edenberg HJ, Foroud T, et al. Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: preliminary results from the COGA project. Alcoholism: Clinical and Experimental Research 1998;22:1317–23.

Raine A, Reynolds C, Venables PH, Mednick SA, Farrington DP. Fearlessness, stimulation-seeking, and large body size at age 3 years as early predispositions to childhood aggression at age 11 years. Archives of General Psychiatry 1998;55:745–51. [PubMed: 9707386]

Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. Psychological Bulletin 2002;128:490–529. [PubMed: 12002699]

Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, et al. Comparison of direct interview and family history diagnoses of alcohol dependence. Alcoholism: Clinical and Experimental Research 1995;19:1018–23.

Rutter, M.; Quinton, D. Psychiatric disorder: ecological factors and concepts of causation. In: McGurk, H., editor. Ecological Factors in Human Development. Amsterdam; North Holland: 1977. p. 173-87.

Schuckit, MA. Vulnerability factors for alcoholism. In: Davis, K., editor. Neuropsychopharmacology: The Fifth Generation of Progress, Chapter 98. Baltimore, MD: Lippincott Williams & Wilkins Co; 2002. p. 1399-1411.

Schuckit MA. An overview of genetic influences in alcoholism. Alcoholism: Clinical and Experimental Research. in press

Schuckit MA, Gold EO. A simultaneous evaluation of multiple markers of ethanol/placebo challenges in sons of alcoholics and controls. Archives of General Psychiatry 1988;45:211–16. [PubMed: 3422553]

Schuckit MA, Smith TL. An 8-year follow-up of 450 sons of alcoholics and control subjects. Archives of General Psychiatry 1996;53:202–10. [PubMed: 8611056]

Schuckit MA, Smith TL. The relationships of a family history of alcohol dependence, a low level of response to alcohol and six domains of life functioning to the development of alcohol use disorders. Journal of Studies on Alcohol 2000;61:827–35. [PubMed: 11188488]

Schuckit MA, Smith TL. The relationship of behavioral undercontrol to alcoholism in higher-functioning adults. Drug and Alcohol Review 2006;25:393–402. [PubMed: 16939933]

Schuckit MA, Danko GP, Smith TL. Patterns of drug-related disorders in a prospective study of men chosen for their family history of alcoholism. Journal of Studies on Alcohol 2004;65:613–20. [PubMed: 15536771]

Schuckit MA, Kelsoe JR, Braff DK, Wilhelmsen KC. Some possible genetic parallels across alcoholism, bipolar disorder, and schizophrenia. Journal of Studies on Alcohol 2003a;64:157–59. [PubMed: 12713187]

Schuckit MA, Smith TL, Barnow S, Preuss U, Luczak S, Radziminski S. Correlates of externalizing symptoms in children from families of alcoholics and controls. Alcohol and Alcoholism 2003b; 38:559–67. [PubMed: 14633643]

Schuckit MA, Smith TL, Danko GP, Reich T, Bucholz KK, Bierut LJ. Similarities in the clinical characteristics related to alcohol dependence in two populations. American Journal on Addictions 2002;11:1–9. [PubMed: 11876579]

Schuckit MA, Smith TL, Kalmijn JA, Raimo EB. The relationship of a low response to alcohol to ERP and personality measures. Alcoholism: Clinical and Experimental Research 2000a;24:27A.

Schuckit MA, Smith TL, Radziminski S, Heyneman EK. Behavioral symptoms and psychiatric diagnoses among 162 children in nonalcoholic or alcoholic families. American Journal of Psychiatry 2000b; 157:1881–83. [PubMed: 11058493]

Scourfield J, van den Bree M, Martin N, McGuffin P. Conduct problems in children and adolescents: A twin study. Archives of General Psychiatry 2004;61:489–96. [PubMed: 15123494]

Seljamo S, Aromaa M, Koivusilta L, Rautava P, Sourander A, Helenius H, et al. Alcohol use in families: a 15-year prospective follow-up study. Addiction 2006;101:984–92. [PubMed: 16771890]

Sher, KJ. Children of Alcoholics: A Critical Appraisal of Theory and Research. Chicago: University of Chicago Press; 1991.

Slutske WS, Heath AC, Dinwiddie SH, Madden PAF, Bucholz KK, Dunne MP, et al. Common genetic risk factors for conduct disorder and alcohol dependence. Journal of Abnormal Psychology 1998;107:363–74. [PubMed: 9715572]

Span SA, Earleywine M. Cognitive functioning moderates the relation between hyperactivity and drinking habits. Alcoholism: Clinical and Experimental Research 1999;23:224–29.

Spitzer, RL.; Endicott, J. Schedule for Affective Disorders and Schizophrenia. New York: New York State Psychiatric Institute; 1977.

Spitzer RL, Williams JBW, Gibbon M, First MD. The structured clinical interview for DSM-III-R (SCID). Archives of General Psychiatry 1992;49:624–29. [PubMed: 1637252]

Tarter RE, Kirisci L, Habeych M, Reynolds M, Vanyukov M. Neurobehavior disinhibition in childhood predisposes boys to substance use disorder by young adulthood: direct and mediated etiologic pathways. Drug and Alcohol Dependence 2003;73:121–32. [PubMed: 14725951]

Thapar A, Harrington R, McGuffin P. Examining the comorbidity of ADHD-related behaviours and conduct problems using a twin study design. British Journal of Psychiatry 2001;179:224–29. [PubMed: 11532799]

Thapar A, Langley K, Fowler T, Rice F, Turic D, Whittinger N, et al. Catechol O-methyltransferase gene variant and birth weight predict early-onset antisocial behavior in children with attention-deficit/hyperactivity disorder. Archives of General Psychiatry 2005;62:1275–78. [PubMed: 16275815]

Todd RD, Rasmussen ER, Neuman RJ, Reich W, Hudziak JJ, Bucholz KK, et al. Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. American Journal of Psychiatry 2001;158:1891–98. [PubMed: 11691697]

Westermeyer J, Thuras P. Association of antisocial personality disorder and substance disorder morbidity in a clinical sample. The American Journal of Drug and Alcohol Abuse 2005;1:93–110. [PubMed: 15768573]

Wozniak J, Biederman J, Faraone SV, Blie H, Monuteaux MC. Heterogeneity of childhood conduct disorder: further evidence of a subtype of conduct disorder linked to bipolar disorder. Journal of Affective Disorders 2001;64:121–31. [PubMed: 11313079]

Zucker, RA.; Ellis, D.; Bingham, CR.; Fitzgerald, HE. The development of alcoholic subtypes risk variation among alcoholic families during the early childhood years. In: Abbott, S., editor. Children of Alcoholics: Selected Readings. II. Rockville, MD: National Association of Children of Alcoholics; 2000. p. 243-64.

Table 1

Demography, Family History, and Psychiatric Outcomes for Offspring with and without Externalizing Conditions

	Externalizing	No Externalizing	t or χ^2	p-value
Sample Size	17	148		
Age	18.2 (3.75)	17.5 (2.90)	−1.0	.31
Father's Education	18.4 (2.47)	18.1 (2.19)	−0.4	.69
Mother's Education	14.2 (1.99)	15.5 (2.49)	2.04	<.05
Family Monthly Income	10,647.1 (7,158.40)	10,560.8 (6,947.06)	−0.05	.97
Sex (% Male)	88.2%	47.3%	10.2	.001
Offspring Race (% Caucasian)	82.4%	98.6%	13.78	<.001
Divorced Parents	41.2%	13.5%	8.5	.004
Offspring Psychiatric Diagnosis (%)				
CD	58.9%	0.0%		
ADHD	41.1%	0.0%		
Major Depression	0.0%	3.4%	0.59	.44
Bipolar Disorder	0.0%	1.4%	0.23	.63
Anxiety Disorders	11.8%	2.7%	3.57	.06
Other	5.9%	0.7%	3.45	.07
Offspring FH (%)				
Alcohol Use Disorder	29.4%	34.5%	0.17	.68
Substance Use Disorder	5.9%	16.9%	1.39	.24
Any Psychiatric Diagnosis	47.1%	34.5%	1.05	.31
Major Depression	35.3%	27.7%	0.43	.51
Bipolar Disorder	17.6%	2.0%	10.62	<.01
Anxiety Disorder	0.0%	4.1%	0.72	.40

Table 2

Substance Use Histories for Offspring with and without Externalizing Conditions

	Externalizing	No Externalizing	t or χ^2	p-value
Sample Size	17	148		
Alcohol				
Ever Drank (%)	58.8%	53.4%	0.18	.67
Max Drinks Lifetime	11.5 (3.46)	6.8 (4.37)	−2.91	.006
Usual Frequency (6 mo.)	1.8 (1.97)	1.3 (1.45)	−1.05	.30
Usual Quantity (6 mo.)	3.3 (3.41)	1.4 (1.80)	−2.53	.02
Ever Alcohol Problems (%)	87.5%	44.3%	5.37	.03
Diagnosis Abuse/Dependence (%)	23.5%	6.8%	5.53	.02
Abuse	5.9%	0.7%	3.45	.07
Dependence	17.6%	6.1%	3.03	.09
Drugs				
Nicotine				
Ever use	17.6%	21.6%	0.1	.70
Dependence	5.9%	0.0%	8.76	.004
Marijuana				
Ever use	47.1%	30.4%	1.9	.17
Abuse/Dependence	29.4%	6.1%	10.69	.002
Cocaine				
Ever use	29.4%	8.1%	7.5	.006
Abuse/Dependence	5.9%	0.0%	8.76	.004
Amphetamines				
Ever use	11.8%	7.4%	0.4	.53
Abuse/Dependence	5.9%	2.0%	0.96	.33
Hallucinogens				
Ever use	41.2%	10.1%	12.7	<.001
Abuse/Dependence	5.9%	1.4%	1.75	.19
Sedatives/Hypnotics				
Ever use	17.6%	3.4%	6.7	.009
Abuse/Dependence	0.0%	0.0%	na	na
Opiates				
Ever use	5.9%	5.4%	.01	.94
Abuse/Dependence	5.9%	1.4%	1.75	.19

Table 3

Hierarchical Logistic Regression Using Significant Variables (Odds Ratios) from Table 1 to Predict CD or ADHD Diagnosis

Variables	CD or ADHD Diagnosis
Female Sex	6.21[a]
Non-Caucasian	12.35[a]
Divorced Parents	4.37[a]
Bipolar FH	11.51[a]
R^2 change (%)*	5.7[a]
Pseudo-R^2 (%)	32.3[c]

[a] = p < .05;

[b] = p < .01;

[c] = p < .001

* Bipolar FH as second step

Table 4

Demography, Family History, and Psychiatric Outcomes for Offspring with and without Alcohol and/or Drug Diagnosis

	Alcohol/Drug DX	No Alcohol/Drug DX	t or χ^2	p-value
Sample Size	20	145		
Age	20.6 (2.59)	17.1 (2.81)	−5.16	<.001
Father's Education	17.5 (2.33)	18.2 (2.19)	1.39	.17
Mother's Education	14.4 (2.64)	15.5 (2.42)	1.92	.06
Family Monthly Income	6450.0 (4,650.69)	11137.9 (7030.31)	2.89	<.01
Sex (% Male)	70.0%	49.0%	3.11	.08
Offspring Race (% Caucasian)	95.0%	97.2%	0.30	.58
Divorced Parents	45.0%	12.4%	13.64	<.001
Offspring Psychiatric Diagnosis (%)				
CD	35.0%	2.1%	33.48	<.001
ADHD	0.0%	6.2%	1.31	.26
Major Depression	10.0%	2.1%	3.76	.06
Bipolar Disorder	5.0%	0.7%	2.73	.10
Anxiety Disorders	5.0%	3.4%	0.12	.73
Other	5.0%	0.7%	2.73	.10
Offspring FH (%)				
Alcohol Use Disorder	50.0%	31.7%	2.62	.11
Substance Use Disorder	30.0%	13.8%	3.48	.07
Any Psychiatric Diagnosis	35.0%	35.9%	0.01	.94
Major Depression	20.0%	29.7%	0.80	.38
Bipolar Disorder	15.0%	2.1%	8.39	.005
Anxiety Disorder	5.0%	3.4%	0.12	.73

Table 5

Hierarchical Logistic Regression Using Significant Variables (Odds Ratios) from Table 4 to Predict Alcohol and Drug Use Disorders

Variables	Alcohol and/or Drug Diagnosis
Age	1.50[c]
Income (in units of $1,000)	0.81[a]
Divorced Parents	3.77
Bipolar FH	1.78
Conduct disorder	18.04[a]
R^2 change (%)*	5.7[a]
Pseudo-R^2 (%)	51.3[c]

[a] = p < .05;

[b] = p < .01;

[c] = p < .001

* Conduct Disorder as second step