Novelty Seeking as a Moderator of Familial Risk for Alcohol Dependence

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Background: Disinhibitory personality traits such as high novelty seeking (NS) are moderately heritable, and individuals with substance use disorders (SUDs) frequently exhibit such traits. However, recent studies have cast doubt on the supposition that such traits are true familial risk factors for SUD and particularly for alcohol dependence. Another possibility is that familial risk interacts with personality-associated risk, in which case the association between personality and familial risk might depend on sample composition, accounting for the lack of consensus among studies to date. We examined this possibility by analyzing the association between NS and alcohol dependence in individuals at intermediate and high levels of familial risk for alcohol dependence.

Methods: Data from the Collaborative Study on the Genetics of Alcoholism, a multisite family study, were examined. Subjects were 1,111 adult siblings of alcohol-dependent index cases. Parental diagnoses of alcohol dependence and personality scores of NS from the Tridimensional Personality Questionnaire were used to predict alcohol dependence.

Results: A significant interaction between NS and familial risk for alcoholism was seen, such that NS was a significantly stronger predictor of alcohol dependence in subjects with one or more parents with alcohol dependence than in subjects without alcohol-dependent parents.

Conclusions: Novelty seeking and familial risk interact so that the risk associated with high NS is magnified in families with parental alcohol dependence and NS is a moderator of familial risk. Accordingly, high NS is strongly associated with alcohol dependence in subjects with a parent diagnosed with alcohol dependence, but low NS may protect against the risk associated with familial alcoholism. This interaction may account for conflicting findings from studies that have examined this question previously.

Key Words: Personality, Substance Use Disorders, Alcohol Dependence, Family Study.

NUMEROUS LONGITUDINAL STUDIES have shown novelty seeking (NS) and related disinhibitory personality traits to be antecedents of substance use, abuse, and dependence (Cloninger et al., 1988; Masse and Tremblay, 1997; Newcomb and McGee, 1991; Pedersen, 1991; Teichman et al., 1989). Given that personality is moderately heritable and is a precursor of substance-related disorder, it would seem likely that personality traits are familial risk factors for substance use disorders (SUDs), i.e., that SUD-associated personality traits are transmitted in families along with risk for SUDs. If this is true, members of families with a high density of SUDs would be expected to differ from members of lower-density families on personality traits associated with SUDs. Moreover, such differences should be apparent even when comparing unaffected individuals from different family backgrounds (Elkins et al., 2004; Farmer et al., 2003; Swendsen et al., 2002). This is because individuals from densely affected families are more likely than individuals from lower-risk families to carry heritable risk factors (i.e., personality) even if they are not affected themselves [A more quantitative exposition of such phenomena has been published by DiLalla et al. (2000)]. However, findings from family studies of SUDs have not consistently found personality differences between unaffected family members from different family backgrounds.

In a family study focused on SUDs of all types, Swendsen et al. (2002) examined the personality traits of first-degree relatives of individuals with SUDs and compared them with first-degree relatives of individuals without SUDs. The personality trait of constraint (similar to NS, reversed in sign) in adult first-degree relatives of individuals with SUDs was compared with first-degree

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Received for publication December 1, 2005; accepted February 27, 2006.

Support: NIH-K01DA16618 (RAG) and the Collaborative Study on the Genetics of Alcoholism (NIH-U10AA08401).

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DOI: 10.1111/j.1530-0277.2006.00133.x

relatives of unaffected individuals; probands and relatives were also stratified by the presence or absence of SUDs. Although affected relatives of individuals with SUD scored lower in constraint than affected relatives of individuals without SUD, no difference was detected when unaffected relatives from these 2 groups were compared. Because differences in personality measurements were not observed when unaffected relatives were compared, the authors argued that disinhibitory personality traits might be involved in the etiology of SUDs, but that such traits may not constitute familial risk factors. This is a surprising finding, given that both personality disorders and SUDs are heritable and that disinhibitory personality traits emerge before alcohol and other drug use disorders in nonfamilial longitudinal designs (Bierut et al., 1998; Cloninger et al., 1988; Gillespie et al., 2003; Masse and Tremblay, 1997; Newcomb and McGee, 1991; Pedersen, 1991; Stallings et al., 1996; Teichman et al., 1989). Thus, the results of Swendsen et al. (2002) indicate that the association between SUDs, disinhibitory personality, and family risk factors may be more complex than anticipated.

Other family-based study designs have addressed the question of disinhibitory personality traits and their relation to familial risk. In an analysis of individuals who had not yet passed through the period of SUD risk, Elkins et al. (2004) showed that constraint scores were lower in 17-year-old offspring of parents with drug dependence or comorbid alcohol/drug dependence, even when offspring with SUD were excluded from the analysis. However, this effect was not seen in the offspring of parents with alcohol dependence only. Two studies have reported elevated NS scores in the offspring of alcoholic parents, but these studies did not test whether the effect remained when affected offspring were excluded from the analyses (Ravaja and Keltikangas-Jarvinen, 2001; Sher et al., 1991). Therefore, the question of whether or not disinhibitory personality traits are associated with familial risk for SUDs, and in particular for alcohol use disorders, merits further investigation.

Personality traits in childhood have been invoked as moderating factors, rather than direct risk factors, for a variety of outcomes (Blackson et al., 1996; Chess et al., 1963; Rutter, 1987; Wong et al., 1999). If such phenomena extend to adults, disinhibitory personality traits may be important as moderators of familial risk in addition to, or instead of, being direct risk factors. In the case of SUDs, this would correspond to an interaction between personality and familial risk in the prediction of disorder, but it would also mean that the association between personality and familial risk is complex and could vary as a function of disease state. In this case, the association between personality and familial risk in a given sample would depend on the prevalence of SUDs in a sample, and not all studies would find significant associations.

The purpose of the present study is to extend previous studies addressing disinhibitory personality traits as familial risk factors for SUDs by examining the 3-way associations among personality, familial risk, and alcohol dependence. Our focus is on the personality trait of NS, a scale whose association with both alcohol and drug use disorders is well documented (e.g., Barnes et al., 2000; Cloninger et al., 1988; Conway et al., 2002; Howard et al., 1997; Sher et al., 1991). We explicitly consider the possibility of an interaction between personality and familial risk for alcoholism by hypothesizing that NS is a stronger risk factor for alcohol dependence among individuals with high familial risk for alcohol dependence than among individuals with lower familial risk.

METHODS

Overview

Data from a large family study of alcoholism, the Collaborative Study on the Genetics of Alcoholism (COGA), were utilized. Our analyses examined NS and alcohol dependence in siblings of alcohol-dependent probands from 2 different familial risk groups. One group is at high risk because there is an alcohol-dependent proband and at least 1 parent with alcohol dependence. Another group is at somewhat lower risk because there is an alcohol-dependent proband but neither parent is dependent (referred to as ''medium risk''). As outcome variables, we used a standard dichotomous classification of alcohol dependence and also considered ''problem drinking,'' that is, 1 or more symptoms of alcohol abuse or dependence on a lifetime basis, as an intermediate diagnostic category. We present results for both categorizations for all major analyses. The COGA is a multisite family and genetic study that collects data on a broad variety of behavioral variables, risk factors and psychiatric diagnoses as well as genetic and biological variables. Data for these analyses were collected from 6 study sites: Indiana University Medical School (Indianapolis), State University of New York Health Sciences Center at Brooklyn, University of California at San Diego, University of Connecticut (Farmington), University of Iowa (Iowa City), and Washington University in St. Louis. Subjects were recruited from inpatient and outpatient chemical dependency treatment units. To qualify for the study, probands were required to meet criteria for both *Diagnostic and Statistical Manual*—Third Edition—Text Revision (DSM-III-R) alcohol dependence and Feighner alcoholism (Feighner et al., 1972) and to have 2 first-degree relatives living within 1 of the 6 catchment areas for the study. For these analyses, we focused on alcohol-dependent case families who have largely passed through the period of risk for developing alcohol dependence (mean age = 34.7, SD = 7.7). Community-recruited comparison families were not included because the age distribution is substantially younger (mean = 26.7, SD = 6.5); these individuals have not passed through the risk period and direct comparison with the treatment-recruited families would not have been appropriate for these analyses.

Subjects

Analyses utilized data for adult siblings of alcohol-dependent COGA probands with complete diagnostic interview and personality data. In our primary analyses, we included siblings for whom direct interviews were available for both parents. To determine whether there was bias introduced by this requirement, a second set of analyses was conducted on a larger group of sibling sets with parents who were not available for direct interview, but for whom family history information on the parents was available.

Because alcohol dependence was the outcome of interest, and drug dependence often exhibits similar correlates, siblings were excluded if

they met criteria for drug dependence but not alcohol dependence (100 individuals from 35 families excluded). Likewise, if the sibling's parents did not exhibit alcohol dependence, but 1 or more qualified for a diagnosis of drug dependence, the family was excluded (5 individuals from 2 families excluded). After exclusions, direct interview data were available for 429 families consisting of 1,111 siblings of probands, their mothers, and their fathers. Each family contained an average of 2.6 siblings of probands (SD = 1.3).

Assessments

Diagnostic information for siblings was obtained using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA). The SSAGA is a lay-administered interview designed to assess alcohol abuse and dependence, other substance use, and psychiatric disorders over a lifetime. It has been shown to be highly reliable and to exhibit acceptable concordance with clinician-administered interviews (Bucholz et al., 1994; Hesselbrock et al., 1999). Lifetime parental diagnoses of DSM-III-R alcohol dependence were obtained using SSAGA for the primary set of analyses. For the second set of analyses, which incorporated families for whom parents were not available for direct interview, the Family History Assessment Module (FHAM) was used to assign missing lifetime parental diagnoses (Janca et al., 1991); the FHAM has been shown to be useful as a proxy for direct interview data (Rice et al., 1995). Reports from siblings and coparents in the primary data set were used to impute alcohol dependence diagnoses for uninterviewed parents. A positive diagnosis was imputed if reports from one or more relatives indicated the parent met diagnostic criteria for alcohol dependence.

Novelty seeking was assessed using Cloninger's Tridimensional Personality Questionnaire (TPQ; Cloninger, 1986). The TPQ NS scale has been shown to exhibit good internal and test–retest reliability (Cloninger et al., 1991). Scores were adjusted for age and gender and normalized according to 1987 U.S. normative data from a nationally representative sample (Cloninger et al., 1991). Norm-based scores are reported based on a U.S. mean value of 0 and a standard deviation (SD) of 100, i.e., the adjusted Z-score multiplied by 100. Odds ratios (ORs) for NS scores reported in logistic regression results correspond to risk associated with a 1 SD difference in the personality score.

Diagnoses and Categories

Lifetime diagnoses for alcohol and drug dependence for siblings and their parents were made based on SSAGA interview data using DSM-III-R criteria. All analyses were run with the standard dichotomous diagnostic classification in addition to a 3-category classification that included "problem drinkers" as an intermediate category. Problem drinkers comprised individuals who met one or more criteria for DSM-III-R lifetime alcohol abuse or dependence but did not meet full criteria for dependence. Individuals who did not meet any criteria for DSM-III-R alcohol abuse or dependence in their lifetime were categorized as "abstinent/moderate" drinkers. This category included lifetime abstainers ($n = 14$ or 1.1% of the sample).

Statistical Methods

In all analyses, siblings of COGA probands with one or more parents with a diagnosis of alcohol dependence (high-risk family) were compared with siblings without affected parents (medium-risk family). Wald- chi-square for frequency tables of risk category by diagnostic outcome were computed using logistic or multinomial logistic regression. Linear models [analysis of variance (ANOVA)] were used to examine the association between familial risk category and NS both in the sample as a whole and stratified by either dichotomous diagnosis or 3-category outcome. Regression lines derived from stratified ANOVAs were used for graphical analysis of NS as a function of familial risk. A graphical analysis of the prevalence of alcohol dependence and problem drinking as a function of NS, stratified by parent diagnosis, was also carried out. For that analysis only, NS was converted to an ordinal variable; individuals in the bottom quartile of the sample (25th percentile or below) in terms of NS score were classified as "low," those in the middle 2 quartiles (26th–75th percentiles) were classified as "moderate," and those in the top quartile of the sample (76th percentile and above) were classified as "high."

To formally test for the presence of an interaction, logistic regression was used to calculate ORs associated with NS in the prediction of alcohol dependence, with age and gender included as covariates and incorporating terms for familial risk category and the interaction between familial risk and NS. Similar analyses were carried out using the 3-category classification as the outcome. The latter analyses utilized multinomial logistic regression. This technique is similar to standard logistic regression, except that multicategory outcomes are allowed with separate ORs and hypothesis tests computed for each outcome category, relative to a reference category. For this analysis, abstinent/moderate drinkers were considered to be the baseline or reference group. Age and gender of the siblings were included as covariates in both sets of logistic regression analyses.

Calculations were carried out using the Stata and SAS systems (SAS Institute Inc., 1999–2000; Stata Corporation, 1997). Standard errors and hypothesis tests were calculated using the Huber/White/sandwich robust estimator of variance (Stata) to account for clustered sampling of families.

RESULTS

Demographics

Our analyses focused on siblings of individuals recruited through a diagnosis of alcohol dependence. Of this sample, 44% were male and 56% were female; 11% were African American; 84% were Caucasian; 5% belonged to other ethnic/racial groups; 8% of the sample had fewer than 12 years of education; 38% had a high school diploma or equivalent; 54% had education beyond high school; 55% were married; 16% were separated, widowed or divorced; and 29% were never married. The average age of the sample of siblings at the time of the main assessment battery was 34.7 years (median = 35, SD = 7.7).

Prevalence of Alcohol Dependence and Comorbid Disorders Versus Familial Risk

Parent diagnosis was used as an indicator of familial risk for alcohol dependence: siblings of alcohol-dependent probands with one or both parents affected are labeled as "high risk"; siblings of alcohol-dependent probands with neither parent affected are labeled as "medium risk." Table 1 lists the populations and proportions of individuals from each risk group comprising the full sample, the alcohol-dependent and nondependent strata, and the membership of each category within the 3-category alcohol classification, which further divides the nondependent strata into problem drinkers and abstinent/moderate drinkers (see Methods for precise definitions). Not surprisingly, familial risk is significantly associated with alcohol outcome using either alcohol categorization.

Table 1. Distribution of Siblings by Familial Risk Category

	Medium-risk families		High-risk families	
	N	%[a]	*N*	%
Full sample	571	51.4	540	48.6
Diagnosis				
Non-alcohol dependent	366	64.1	249	45.1
Alcohol dependent	205	35.9	291	53.9
Wald-χ^2 (*df*)/*p*				27(1)/$p<0.001$
Three-stage classification				
Moderate/abstinent drinkers	218	38.2	122	22.6
Problem drinkers	148	25.9	127	23.5
Alcohol dependent	205	35.9	291	53.9
Wald -χ^2 (*df*)/*p*				43(2)/$p<0.001$

[a]Correponds to column percentages for multiway entries.

Table 2. Novelty Seeking (×100 *Z*-score) as a Function of Familial Risk Category

	Medium-risk families (571 siblings)	High-risk families (540 siblings)		
	Mean NS (SE)	Mean NS (SE)	|*t*|	*p*
Full sample	19.6 (4.2)	39.6 (4.8)	2.9	0.004
Diagnosis				
Non-alcohol dependent	11.2 (5.1)	6.8 (6.4)	0.5	0.61
Alcohol dependent	34.4 (7.2)	67.5 (6.5)	3.4	0.001
Three-stage classification				
Abstinent/moderate drinkers	11.1 (6.7)	−10.6 (9.2)	1.9	0.06
Problem drinkers	11.4 (7.7)	23.6 (8.9)	1.0	0.32
Alcohol dependent	34.4 (7.3)	67.5 (6.5)	3.6	<0.001

High-risk siblings with alcohol dependence also exhibited higher symptom counts (mean = 5.5, SE = 0.1) compared with those from medium-risk families (mean = 5.0, SE = 0.1). High-risk siblings have a higher prevalence of drug dependence; 14.4% of high-risk siblings versus 8.8% of medium-risk siblings have comorbid drug dependence (Wald -$\chi^2 = 17.0$, $p<0.001$; siblings with drug dependence alone were excluded; see Methods). The most common drug dependencies for both high-risk and medium-risk siblings are cocaine (31.4 and 21.5%, respectively) and marijuana (22.4 and 14.4%, respectively). There is a higher prevalence of antisocial personality disorder (ASPD) among high-risk siblings; 5.9% of high-risk siblings have ASPD compared with 1.9% of medium-risk siblings (Wald -$\chi^2 = 24.4$, $p<0.001$).

Characteristics of High-Risk Versus Medium-Risk Parents

In high-risk families, 12.2% of siblings had one or both parents with drug dependence (parents in medium-risk families do not have drug dependence by definition). Likewise, 8.8% of high-risk siblings have one or more parents with ASPD whereas only 1 medium-risk sibling (0.2%) has a parent with ASPD (Wald -$\chi^2 = 19.2$, $p<0.001$).

Novelty Seeking Scores

Table 2 lists the mean values of NS, *Z*-scored according to U.S. normative data, for offspring within each familial risk group. Siblings from high-risk families have elevated NS scores compared with siblings from medium-risk families ($\beta = 19.6$, SE = 6.8, $t = 2.89$, $p = 0.004$). To test whether this effect was a result of comorbid parental drug dependence or antisocial personality disorder rather than parental alcohol dependence, 2 additional ANOVA analyses were conducted that tested the effects of each of these variables as predictors in addition to parent alcohol dependence (all parents with drug dependence have comorbid alcohol dependence; see Methods). The effect of parent drug dependence on NS approached significance ($\beta = 29.0$, SE = 17.0, $t = 1.7$, $p = 0.084$), but the alcohol dependence effect was little changed ($\beta = 16.7$, SE = 7.0, $t = 2.4$, $p = 0.02$). Likewise, the effect of parent ASPD approached significance ($\beta = 22.7$, SE = 12.4, $t = 1.8$ $p = 0.072$) but had little influence on the parental alcoholism effect ($\beta = 15.0$, SE = 7.2, $t = 2.1$, $p = 0.02$) Therefore, the association between parent alcohol dependence and offspring NS cannot be attributed to comorbid parent drug dependence or ASPD.

Although individuals from medium-risk and high-risk families differ on NS, stratification by individuals' own alcohol dependence diagnosis or by the 3-category alcohol classification shows that the difference is significant only among individuals with alcohol dependence (Table 2). Yet, the correlation between NS and familial risk varies with disease state, suggesting an interaction between NS, familial risk, and disease state. This is especially clear when the data are examined graphically, as shown in Fig. 1A, with the sample stratified according to the 3-category classification. Among alcohol-dependent subjects, individuals from high-risk families have significantly higher NS scores than those from medium-risk families. In contrast, the difference in NS between familial risk categories (corresponding to the slope in Fig. 1A) exhibits a nearly significant *negative* trend in abstinent/moderate drinkers; i.e., abstinent/moderate drinking individuals from high-risk families have slightly *lower* NS scores than their counterparts from medium-risk families (see Table 2 for statistics). A nonsignificant positive trend is observed for problem drinkers. Overall, in high-risk families, the differences in NS between abstinent/moderate drinkers, problem drinkers, and alcohol-dependent individuals are larger than in medium-risk families. Likewise, the association between NS and alcohol dependence or problem drinking depends on familial risk. In Fig. 1B, NS scores are categorized as high (highest scoring 25% of full sample), moderate (middle scoring 50% of full sample) or low (lowest scoring 25% of full sample) and stratified by familial risk category. The trend toward higher rates of problem drinking and alcohol dependence at higher NS levels is much stronger in the high-risk group than in the medium-risk group.

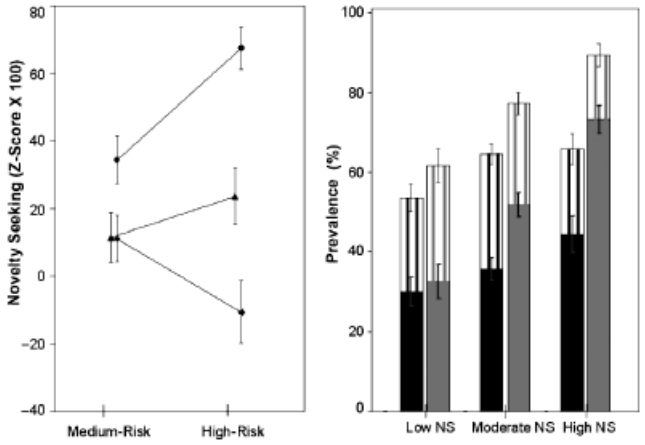

Fig. 1. (**A**) Novelty seeking (NS) scores of Collaborative Study on the Genetics of Alcoholism siblings as a function of familial risk: circle, alcohol dependent ($n = 291$); triangle, problem drinkers ($n = 127$); diamond, abstinent/moderate drinkers ($n = 122$). Solid lines were calculated from regression parameters. (**B**) Prevalence of alcohol-related outcomes as a function of NS, stratified by familial risk. Black, high risk; gray, medium risk. Solid bars, alcohol dependence; striped bars, problem drinking (abstinent/moderate drinkers omitted for clarity). Low NS corresponds to 25% of the sample lowest in NS ($n = 157$ medium-risk and 120 high-risk individuals, respectively), Moderate NS is the middle 50% ($n = 297$ and 259), and high NS is the top 25% ($n = 117$ and 161). Error bars for both figures correspond to standard errors.

Accordingly, differences in the rates of alcohol problems and dependence between high-risk and medium-risk families are very apparent in the high NS group but are diminished in the low NS group.

Interaction Between NS and Familial Risk

To formally test the significance of the putative interaction, we used logistic regression to predict alcohol dependence from NS, familial risk category, and the interaction between the two. Age and gender of the siblings were included as covariates as both are known to be related to alcohol dependence and NS (Bucholz, 1999; Cloninger et al., 1991). The results of these analyses are shown in Table 3, which shows ORs associated with familial risk category, NS, and the interaction between the two. Novelty seeking and interaction ORs correspond to the odds increments associated with a 1-SD change in NS. For example, an individual from a medium-risk family with NS that is 1 SD above the sample average has 33% higher odds of alcohol dependence than a medium familial risk individual whose NS score is at the sample average. Both NS and familial risk are associated with alcohol dependence and there is significant interaction between the two (interaction OR = 1.34, $p = 0.02$). Age and gender were both significant covariates (OR = 0.87 per 10 years of age, $p = 0.009$; OR = 3.7 for males vs females, $p < 0.001$). The analysis was repeated with the dichotomous diagnosis replaced by the 3-category classification using multinomial (multiple-outcome) logistic regression. Novelty seeking and familial risk are significantly associated with alcohol dependence, and there is a significant interaction between the two (interaction OR = 1.60, $p = 0.002$). Hence, the association between NS and alcohol dependence is modest in medium-risk families (OR = 1.35) but is about 60% stronger in the high-risk families (OR = 2.14, $p < 0.001$). Relative to abstinent/moderate drinkers, NS is not associated with problem drinking in medium-risk families, but familial risk category does predict problem drinking. Moreover, because there is a significant interaction between NS and familial risk (interaction OR = 1.37, $p = 0.05$), there is a significant association between NS and problem drinking for individuals from high-risk families (OR = 1.39, $p = 0.003$).

Table 3. Logistic Regression Results for Prediction of Alcohol Dependence or Problem Drinking From Novelty Seeking, Familial Risk, and Their Interaction

	OR	(95% CI)	*p*
Model I: Dichotomous diagnosis			
Alcohol dependence versus no alcohol dependence			
Novelty seeking (per SD)	1.33	(1.11–1.59)	0.002
Family risk status (high vs medium)	1.76	(1.29–2.39)	<0.001
Interaction	1.34	(1.04–1.73)	0.02
Model II: Three-Category Classification			
A. Alcohol dependence versus abstinent/moderate drinking			
Novelty seeking (per SD)	1.35	(1.09–1.65)	0.005
Family risk status (high vs medium)	2.11	(1.46–2.07)	<0.001
Interaction	1.60	(1.19–2.15)	0.002
B. Problem drinking versus abstinent/moderate drinking			
Novelty seeking (per SD)	1.03	(0.82–1.28)	0.80
Family risk status (high vs medium)	1.45	(1.02–2.05)	0.04
Interaction	1.37	(1.00–1.87)	0.05

The presence of an interaction between familial risk and NS implies that NS is a greater risk factor in high-risk families than in medium-risk families. In turn, low NS may confer protection against the risk associated with familial alcoholism. This can be seen by examining Fig. 1B, which plots prevalence of alcohol dependence and problem drinking as a function of NS, stratified by familial risk. Note that among individuals with low NS, the prevalence of alcohol dependence is nearly the same in high-risk families as in medium-risk families. But in the higher NS categories, high-risk family members differ markedly from low-risk family members in rates of problem drinking and alcohol dependence.

Subsidiary Analyses

Two additional logistic regression analyses were conducted to examine the role of potential confounders; for ease of presentation, these analyses were conducted using only the dichotomous diagnosis of alcohol dependence. To ensure that our results do not result from familial comorbidity of drug dependence or ASPD, the logistic regression analysis was repeated with parental and proband diagnoses for these disorders included as covariates. None of the 4 new covariates were significant; ORs associated with

Table 4. Subsidiary Analyses for Prediction of Alcohol Novelty Seeking, Familial Risk, and Their Interaction

	OR	(95% CI)	*p*
Adjusting for familial ASPD, drug dependence			
Novelty seeking (per SD)	1.32	(1.10–1.58)	0.003
Family risk status (high vs medium)	1.82	(1.32–2.50)	<0.001
Parental ASPD	0.99	(0.45–2.18)	0.99
Proband ASPD	1.02	(0.75–1.39)	0.88
Parental drug dependence	0.87	(0.46–1.65)	0.68
Proband drug dependence	1.02	(0.70–1.47)	0.92
Interaction (family risk × NS)	1.35	(1.04–1.75)	0.03
Including families with uninterviewed parents ($N = 2{,}400$)[a]			
Novelty seeking (per SD)	1.51	(1.30–1.75)	<0.001
Family risk status (high vs. medium)	1.57	(1.26–1.94)	<0.001
Interaction (family risk × NS)	1.26	(1.04–1.51)	0.02

[a]Same predictors and covariates as Model I in Table 3.
ASPD, antisocial personality disorder; NS, Novelty seeking.

NS, family risk, and their interaction were largely unchanged (Table 4, top, compared with Table 3, Model I). Because we chose to analyze only families for whom direct interview data were available, there is a possibility that selection bias might be influencing these results. To test this, we repeated the entire set of analyses on a larger set of participants and utilized family history data as a proxy for direct interview data to impute parent diagnoses. This expanded data set contained 2,400 siblings: the original 1,111 siblings whose parents had direct interview data, 886 siblings for whom direct interview was available for 1 parent, and 403 siblings for whom direct data were not available for either parent. The NS main effect was slightly higher (OR = 1.51, $p < 0.001$) whereas the familial risk and interaction effects were slightly lower (OR = 1.57, $p < 0.001$; OR = 1.26, $p = 0.02$, respectively). All of these ORs fall within the 95% confidence intervals of the parameters from the original analysis (Table 3, Model 1). Therefore, the results from the main analyses do not appear to stem from sample selection bias.

DISCUSSION

Summary

Our analyses sought to examine the association between the personality trait NS and alcohol dependence in this large family study of alcoholism. Individuals from families at high risk for alcoholism (defined as having a proband and at least 1 parent with alcohol dependence) had higher overall NS and prevalence of alcohol dependence than subjects from families at medium risk for alcoholism (defined as having a proband with alcohol dependence but no parental alcohol dependence). When siblings were stratified by their own alcohol dependence status, it became clear that the difference in NS between high-risk and medium-risk families is limited to individuals with alcohol dependence. On further examination of the data, a significant interaction between familial risk status and NS was discovered. Novelty seeking and family risk, both independent risk factors, act synergistically so that the risk of high NS is magnified in high-risk families. Additionally, low NS acts as a protective factor against familial alcoholism in these high-risk families.

Comparison With Previously Published Studies

Consistent with the results of Swendsen et al. (2002), we found that NS is associated with familial risk in individuals with alcohol dependence, but not in unaffected individuals. As discussed by those authors, this could be interpreted as evidence that personality change follows the onset of substance dependence, rather than personality traits being familial risk factors. The presence of more severe cases of alcohol dependence in high-risk siblings is consistent with this interpretation; more severe cases correspond to greater personality disturbances. However, our discovery of an interaction between NS and familial risk suggests an alternative explanation. Because of the interaction, one would not necessarily expect to find personality differences in unaffected individuals with different levels of familial risk, even if NS is correlated with familial risk. This can be understood by considering that NS would be a stronger risk factor in higher-risk families than in lower-risk families. Therefore, even moderate levels of NS in high-risk families result in comparatively high risk for alcohol dependence. This would leave the high-risk family unaffected category depleted of individuals with high NS relative to their medium-risk counterparts. In other words, individuals with high NS in higher-risk families advance along the disease development trajectory more readily than they would in a lower-risk family.

Our results extend those of Elkins et al. (2004), who found that disinhibitory personality (low constraint) in offspring personality was predicted by parental drug dependence, but not by parental alcoholism alone. In contrast, we demonstrate that parental alcohol dependence is associated with NS (presumed to be similar to low constraint)[1] even when adjusting for comorbid parent drug dependence. However, the difference in average NS between siblings from high-risk and medium-risk families in our study was small (0.20 SD, see Table 2). In light of the interaction described here between family background and personality, main effect sizes are likely to be small and will depend on the nature of the sample, i.e., the relative proportion of individuals at various levels of familial liability. It may require a very large sample such as the present one to detect such small effects. Therefore, our results do not conflict with those of Elkins and colleagues, who observed a marginally nonsignificant difference in constraint (effect size = 0.23) between high-risk and low-risk offspring.

[1]In a community sample with both constraint and NS scores, the scales are highly correlated ($r = -0.60$; R.A. Grucza and L.R. Goldberg, unpublished analyses; for a description of the sample, see Goldberg, 1999).

Interaction Between NS and Familial Risk

Novelty seeking correlates with familial risk in our sample (Table 2, full sample analysis), but the statistical interaction between NS and familial risk suggests that NS is also a moderator of familial risk. This is in line with the results of several other studies on childhood temperament suggesting that personality or temperament act primarily in concert with other risk factors in predicting a variety of psychopathologies. For example, Rutter (1987) has shown that temperament can influence parental treatment in any given family and is therefore an interactive vulnerability or protective factor for psychopathology. Such a mechanism may be at work in alcoholic families; it has been demonstrated that "risky temperament" in children interacts with familial risk for alcoholism in the prediction of childhood externalizing behavior (Wong et al., 1999). Other studies have demonstrated interactions between adolescent disinhibitory personality factors and child-reported parenting styles in the prediction of substance-related outcomes (Stice and Gonzales, 1998; King and Chassin, 2004).

Presuming a degree of personality continuity between childhood and adulthood, it is possible to speculate about plausible mechanisms for the interaction between NS and parental alcoholism in influencing the development of alcohol problems and dependence. In the absence of parental alcoholism, NS is only moderately associated with adverse alcohol-related outcomes (Table 3). In the family with parental alcoholism, however, intrapersonal factors, such as the personality trait of NS, might interact with parental modeling, the availability of alcohol or any number of other risk factors unique to families of parents with alcohol dependence. In a family with parental alcoholism, risk for alcohol dependence, relative to light/abstinent drinking, is more than doubled for every SD increase in NS.

Limitations

A limitation of this study is that we are dealing only with families in which 1 or more members are affected with alcohol dependence; the subjects in this report are all siblings of alcohol-dependent probands. Therefore, our sample does not include any members of families that are largely unaffected by alcoholism. Having a large number of high-density alcoholic families may have contributed to our ability to identify significant interactions; however, the effect sizes might be different in a general population sample. An additional limitation is that our analyses used only parent diagnoses as indicators of familial risk; hence our results may apply primarily to differences in risk associated with having an alcohol-dependent parent rather than familial density of alcohol dependence in general.

Although our results clearly demonstrate an interaction between NS and familial risk in this population, a number of questions remain open. For example, how strong is the continuity of NS from childhood to adulthood? The development of both NS and alcohol dependence is likely to involve complex combinations of genetic and environmental factors. Hence, it would be desirable to identify more specific factors, such as candidate genes, or particular environmental factors that contribute to the interaction between parental alcohol dependence and NS.

ACKNOWLEDGMENTS

We are grateful to Dr Tom Przybeck for helpful discussions and comments on the manuscript and to Ms Anna Abbacchi for assistance in manuscript preparation.

The Collaborative Study on the Genetics of Alcoholism (COGA) (Principal Investigator: H. Begleiter; Co-Principal Investigators: L. J. Bierut, H. Edenberg, V. Hesselbrock, B. Porjesz) includes 9 different centers where data collection, analysis, and storage take place. The 9 sites and Principal Investigators and Co-Investigators are University of Connecticut (V. Hesselbrock); Indiana University (H. Edenberg, J. Nurnberger Jr, P.M. Conneally, T. Foroud); University of Iowa (S. Kuperman, R. Crowe); SUNY HSCB (B. Porjesz, H. Begleiter); Washington University in St. Louis (L. J. Bierut, A. Goate, J. Rice); University of California at San Diego (M. I. Schuckit); Howard University (R. Taylor); Rutgers University (J. Tischfield); and Southwest Foundation (L. Almasy). Zhaoxia Ren serves as the NIAAA Staff Collaborator.

In memory of Theodore Reich, MD, Co-Principal Investigator of COGA since its inception and one of the founders of modern psychiatric genetics, we acknowledge his immeasurable and fundamental scientific contributions to COGA and the field.

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