
Paternal Alcoholism and Offspring Conduct Disorder: Evidence for the 'Common Genes' Hypothesis

Jon R. Haber,¹ Theodore Jacob,¹ and Andrew C. Heath²

¹*Palo Alto Veterans Affairs Health Care System, Menlo Park, California, United States of America*

²*Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri, United States of America*

Not only are alcoholism and externalizing disorders frequently comorbid, they often co-occur in families across generations; for example, paternal alcoholism predicts offspring conduct disorder just as it does offspring alcoholism. To clarify this relationship, the current study examined the 'common genes' hypothesis utilizing a children-of-twins research design. Participants were male monozygotic (MZ) and dizygotic (DZ) twins from the Vietnam Era Twin Registry who were concordant or discordant for alcohol dependence together with their offspring and the mothers of those offspring. All participants were conducted through a structured psychiatric interview. Offspring risk of conduct disorder was examined as a function of alcoholism genetic risk (due to paternal and co-twin alcohol dependence) and alcoholism environmental risk (due to being reared by a father with an alcohol dependence diagnosis). After controlling for potentially confounding variables, the offspring of alcohol-dependent fathers were significantly more likely to exhibit conduct disorder diagnoses than were offspring of nonalcohol-dependent fathers, thus indicating diagnostic crossover in generational family transmission. Comparing offspring at high genetic and high environmental risk with offspring at high genetic and low environmental risk indicated that genetic factors were most likely responsible for the alcoholism–conduct disorder association. The observed diagnostic crossover (from paternal alcoholism to offspring conduct disorder) across generations in the context of both high and low environmental risk (while genetic risk remained high) supported the common genes hypothesis.

The overrepresentation of children with conduct disorder symptoms or diagnoses in families with an alcoholic parent has remained a consistent finding throughout the past several decades (McGue, 1997; Sher et al., 1991; West & Prinz, 1987; Windle, 1997; Windle & Searles, 1990). However, the origins of this association remain unclear in two important ways. First, although family studies of the children of alco-

holics (COAs) frequently note elevated rates of child conduct disorder problems (Helzer & Pryzbeck, 1988; Lynskey et al., 1994; Stewart et al., 1980; Zucker, 1994), few studies have adequately controlled for potential confounds, and therefore are not conclusive regarding the causal relationship between paternal alcoholism and offspring conduct disorder. In examining this issue, Loukas et al. (2001) reported that the frequent comorbidity between alcoholism and externalizing disorders precluded firm conclusions regarding whether it is specifically parental alcoholism or parental antisocial personality disorder that augmented risk for conduct disorder in children. Given that an antisocial diagnosis is 21 times more likely to occur in an alcoholic versus nonalcoholic population (Zucker, 1994), the likelihood that parental antisociality may confound parental alcoholism in the prediction of offspring conduct disorder is substantial. Furthermore, of those studies that have controlled for parental antisociality, none were designed to distinguish between genetic and environmental influences in evaluation of this association. This report attempts to address these concerns within a novel, highly controlled and genetically informative design.

The many medical and psychosocial consequences of parental alcoholism on the offspring of these families have been repeatedly reported by psychosocial researchers. Family studies have emphasized the impact of family disruption that results in offspring behavior problems and subsequently a developmental trajectory that is associated with negative outcomes (Jacob et al., 2003). Parental alcoholism and parental antisociality, as two separate and additive contributions, can result in child externalizing behaviors (Loukas et al., 2001). During the past several decades, accumulating evidence has indicated that child exter-

Received 12 August 2004; accepted 3 February, 2005.

Address for correspondence: Jon Randolph Haber, Palo Alto Veterans Affairs, Health Care System, 795 Willow Road MC 151-J, Menlo Park, CA 94025-2539, USA. E-mail: rhaber@pgsp.edu

nalizing problems are key precursors of adult externalizing disorders including alcoholism, antisociality, and drug abuse (Windle & Windle, 1993; Zucker et al., 1995). For instance, Caspi et al. (1996) reported that children with externalizing (undercontrolled: impulsive, restless and distractible) behaviors at 3 years of age were significantly more likely than control children to exhibit antisocial personality disorder, and to be involved in crime at 21 years of age. Supporting this finding is a substantial literature indicating that one major pathway to adult alcoholism is through externalizing behaviors in early childhood (Tarter & Vanyukov, 1994; Zucker et al., 1995). In a review of this literature, Zucker (2002, p. 6) concluded that 'a robust group of studies spanning the interval from very early childhood to adulthood strongly implicate behavioral undercontrol as a factor precursive to adult onset of alcohol abuse and dependence'. By identifying a significant, heritable personality factor, Zucker moved the origin of these psychosocial effects to the earliest point in development: genes.

The identification of genetic origins for conduct disorder and alcoholism is supported by behavior-genetic studies which demonstrate that both alcoholism (Heath et al., 1997) and conduct disorder (Krueger et al., 2002; Slutske et al., 1998) are significantly heritable. Most relevant to the association between paternal alcoholism and offspring conduct disorder is Slutske et al.'s (1998) finding that genetic influences account for over 70% of the observed (phenotypic) association between conduct disorder and alcohol dependence, and that 90% of this common genetic risk is associated with behavioral undercontrol personality traits (Slutske et al., 2002). Consistent with earlier psychosocial research, these findings provide strong evidence that genetically transmitted personality factors associated with behavioral undercontrol are causally implicated in the co-occurrence of conduct disorder and alcohol use disorders. This is the common genes hypothesis. Krueger et al.'s (2002) recent work expands on these findings by placing this effect within a larger model of externalizing behaviors, demonstrating that a latent externalizing factor underlies conduct disorder, adolescent antisocial personality traits, alcohol dependence, and illicit substance dependence. His findings indicated an 81% heritability for this common latent externalizing factor, and Kendler et al.'s (2003) recent replication is supportive of these conclusions. The congruence of psychosocial and behavior-genetic research on the importance of genes at the foundation of these effects is noteworthy.

In an earlier study of the transmission of alcoholism risk from parents to children, the authors used a children-of-twins (COT) design to determine the structure of genetic and environmental influences (Jacob et al., 2003). Results indicated that (a) paternal abuse/dependence predicted offspring abuse/dependence; (b) paternal alcohol abuse and paternal alcohol dependence predicted highly similar outcomes for off-

spring; and (c) both genetic and environmental influences were evident in offspring alcohol abuse/dependence outcomes.

In extending this line of inquiry, the current study examined the common genes hypothesis proposed by Slutske et al. (1998, 2002) and Krueger et al. (2002) by assessing transmission of genetic and environmental influences in an alcoholic family context, here defined as a family in which the father satisfied lifetime criteria for alcohol abuse or dependence (here referred to as 'alcoholism'). The current study utilizes a COT research design (Nance & Corey, 1976) as an alternative methodology to the classic twin design in examining genetic structure. Specifically, this study sought to demonstrate that common genes transmitted from parents to children influenced the incidence of offspring conduct disorder as was previously shown to be true of offspring alcoholism (Jacob et al., 2003). The approach was to first examine the phenotypic relationship between paternal alcohol abuse/dependence and offspring conduct disorder. Second, genetic and environmental risk groups would be examined to determine the nature of the common variance between paternal alcoholism and offspring conduct disorder. It was hypothesized that first, families with paternal alcoholism will be associated with increased rates of offspring conduct disorder symptoms (H1); and, second, that families with paternal alcoholism will be associated with increased rates of offspring conduct disorder symptoms in the absence of environmental influences compared to normal control families, thus supporting the hypothesis that common genes account for this association (H2).

Methods

Subjects

The subjects of this study were members of the Vietnam Era Twin Registry (VETR; Eisen et al., 1987), which is comprised of male-male twin pairs born between 1939 and 1957 who served in the United States military between May 1965 and August 1975 (Eisen et al., 1987; Henderson et al., 1990). In 1987, twins completed a mailed questionnaire on general health (Eisen et al., 1991) from which data on their biological offspring, including gender and age, were obtained. In 1992, registry members were administered a telephone psychiatric diagnostic interview covering a range of disorders including alcohol and drug dependence (Harvard Drug Study; Tsuang et al., 1996). For the present study, information from these two studies was used to create a subset of twins based on the following criteria: (1) both twins completed the 1987 and 1992 surveys; (2) at least one twin reported that they had children born between 1974 and 1988; and (3) at least one twin met criteria for a lifetime diagnosis of *Diagnostic and statistical manual of mental disorders*, (3rd ed., rev.); (DSM-III-R, American Psychiatric Association, 1987) alcohol dependence, or both twins were part of a random sample of nonalcohol-dependent control pairs. The

target sample comprised 1464 twins (732 pairs), their biological children and the biological mothers of those children (in rare cases, and only if the biological mother was not involved in rearing the child, a step-mother was substituted if available). Terms of the human subjects approval required that: (1) the twin be contacted first to obtain permission to contact mothers and children; (2) the mothers be contacted next for participation and for permission to contact the children; and (3) the children then be contacted for participation. Of the eligible twins, 1212 (83%) participated in the telephone interview. Participating twins identified and gave consent to contact 1064 mothers of whom 862 (81%) participated in the telephone interview. Consent from both parents to contact their children was obtained for a total of 1487 offspring. Of these, 1270 (85%) participated in the telephone interview. The nonparticipating twins, mothers and offspring were either deceased, unlocatable, unavailable or refused to take part in the study. An average of 82% of those completing the interview returned their mailed questionnaires. In examination of possible attrition bias, father's alcoholism status did not predict whether offspring did or did not participate in the study, and other demographic variables with an association to participation were found to be small in effect size (Scherrer et al., 2003). Therefore, weighting of the data was not conducted.

Procedure

All data collection was performed by interviewers from the Institute for Survey Research (ISR), Temple University in Philadelphia, who received extensive training from both ISR staff and project investigators. Data collection was accomplished by means of an automated Computer Assisted Telephone Interview (CATI) system, which has the advantage of precise standardization of all interview items and probes and the automatic recording of collected information in data files. Fathers, mothers and offspring were interviewed for 45, 60 and 90 minutes respectively and, following the interview, received a questionnaire in the mail.

Assessment Battery

Extensive psychiatric histories of twin fathers had been obtained in 1992 when they participated in the Harvard Drug Study; as a result, assessment for the present study required only a brief interview covering their alcohol use history assessed with a Lifetime Drinking History instrument (Skinner & Schuller, 1982) and a brief assessment of psychiatric symptoms (SCL-30; Derogatis et al., 1974). In addition, a mailed questionnaire assessed parent-child relationships, child's peers, and work and neighborhood information.

The maternal interview, also administered in CATI format, consisted of (1) a self-report; and (2) a report of her participating children. The self-report instrument was an abridged SSAGA-II (Semi-Structured Assessment of the Genetics of Alcoholism) interview developed for the Collaborative Study on the Genetics

of Alcoholism (COGA) project which covered maternal DSM-IV (American Psychology Association, 1994) history of alcohol abuse/dependence and major depression, included screens for drug use, nicotine dependence, mania, antisocial personality, and substance use during pregnancy, and was shown to have excellent test-retest and interrater reliability (Bucholz et al., 1994). In addition, mothers provided a report on each participating child that included birth and early rearing history, child's friends, alcohol and substance use, and assessments of offspring attention deficit/hyperactivity disorder, oppositional/defiant disorder, conduct disorder, as well as child depression and suicide screens. In addition, mothers received a mailed questionnaire identical to fathers.

Participating offspring were also administered an abridged telephone version of the SSAGA interview that permitted determination of DSM-IV (American Psychology Association, 1994) lifetime and current diagnoses of alcohol abuse, alcohol dependence, major depression, childhood conduct disorder, oppositional defiant disorder, anxiety disorders (including social phobia, panic with and without agoraphobia, and generalized anxiety disorders), nicotine dependence, cannabis dependence, and abuse of 7 classes of drugs. In addition, a number of nondiagnostic reports were included assessing school, work and relationship experience, sexual maturation, alcohol history, traumatic events, and relationship quality with friends and siblings. Offspring also received a mailed questionnaire similar to the parents'. The present report focuses on offspring conduct disorder as the outcome of interest.

Children of Twins Design (COT)

The COT design was selected as an alternative methodology for assessing the common genes findings arising from studies using the classical twin methodology. Criticisms of the latter method focus on assumptions and limitations in its procedure for partitioning of variance into genetic, shared environment, and unique environment components. For instance, shared environment is calculated indirectly as the residual of common variance after accounting for genetic variance (Bouchard, 2003; Plomin & Hershberger, 1991), which may lead to overestimates of genetic effects and underestimation of environmental effects. The COT design partitions variance based on participant self-report using assessments of psychiatric symptoms and diagnoses to determine group membership. Hence, genetic and environmental risk factors are measured directly, that is, by measurement or observation of a diagnosis or circumstance. This is a distinctly different means with different assumptions and inferences for partitioning genetic and environmental contributions to the effects of interest, a difference that is particularly important when competing hypotheses are being examined or when an alternative confirmation is required.

The current study operationalized genetic and environmental influences by categorizing participants into

levels of genetic and environmental risk. In the current model, genetic risk was operationalized as an alcohol abuse or dependence diagnosis in the parent (indicating high genetic risk) or the parent's co-twin (indicating high genetic risk if monozygotic [MZ]; intermediate genetic risk if dizygotic [DZ]). Environmental risk was operationalized as the alcohol abuse or dependence status of the twin parent in the home environment; that is, whether the child lived with a father who had ever met criteria for alcohol abuse or dependence.

Data Analysis

Predictor Groups

Twin pairs were classified according to zygosity and alcohol abuse/dependence diagnoses to form four risk groups: group 1 — all twin fathers with a lifetime diagnosis of alcohol dependence or abuse regardless of the alcoholism status of his co-twin; group 2 nonalcoholic fathers with a MZ co-twin having an alcohol dependence diagnosis; group 3 nonalcoholic fathers with a DZ co-twin having an alcohol dependence diagnosis; and group 4 nonalcoholic twin pairs. The normal control reference group, group 4, excluded parents with a diagnosis of alcohol abuse or dependence, but included parents with subclinical symptomatology to limit unrealistic group differences and to enhance generalizability. The classification scheme was intended to create groups that differentiated the level of genetic risk and environmental risk. As can be seen in Table 1, risk decreases sequentially through the groups from group 1 to group 4. Since environmental risk levels are different for offspring of alcoholic twins and their nonalcoholic co-twins, offspring of nonalcoholic discordant twins were categorized into separate environmental risk groups, groups 2 and 3. For genetic influences, risk levels were defined as follows: for twins discordant for alcoholism, the offspring of nonaffected co-twins are included in group 2 if from an MZ pair, and group 3 if from a DZ pair, and the offspring of affected (alcoholic) co-twins are included in group 1. As well, group 1 included the offspring of twins concordant for alcoholism. Thus, all offspring of alcoholic fathers were classified into group 1 regardless of the status of father's co-twin. Confirmation of the homogeneity of genetic liability for alcoholism across the group 1 subgroups is described below. Offspring outcomes could

then be examined across the four risk groups with their respective levels of genetic and environmental risk.

Covariates

A rigorous definition of alcoholism was utilized in that the current study controlled for many potentially confounding variables, most importantly, paternal and maternal antisocial personality and conduct disorder (ASP/CD). It should be noted that to partial out variance associated with parental ASP/CD, one also partials out a component of alcoholism variance that is common to both disorders. The result is a relatively pure alcoholism predictor. However, due to the loss of variance that may be appropriately considered a part of alcoholism variance, this approach reduced statistical power in order to increase clarity of interpretation in the examination of these closely associated variables. Other covariates were paternal conduct disorder; drug abuse; depression; dysthymia; generalized anxiety, panic, and posttraumatic stress disorders; and, for maternal variables, alcohol abuse, alcohol dependence and depression. Although maternal alcoholism may be an important determinant of offspring conduct disorder, this was a low prevalence occurrence in the current sample of high-risk military personnel. However, to control for variation resulting from differences in maternal alcoholism risk across groups, maternal variables (including ASP/CD) were handled as covariates in this design.

Dependent Variable

To maximize statistical power in examining a low-prevalence disorder, an ordinal logistic model was constructed using a four-level dependent variable based on offspring conduct disorder symptoms. The levels were constructed to meet the parallel regression assumption and were tested with the Brant Test (Brant, 1990) with respect to our primary predictor groups; the levels were: (a) 0 and 1 symptom; (b) 2 symptoms; (c) 3 symptoms; and (d) 4 or more symptoms.

Analytic Plan: Group Comparisons

The analysis plan proceeded through two hypotheses. For H1, a significant group 1 elevation in offspring conduct disorder symptoms compared to group 4 normal controls would confirm the phenotypic association between paternal alcoholism and offspring conduct

Table 1

Group by Offspring Genetic and Environmental Risk

	Group 1	Group 2	Group 3	Group 4
	Paternal alcoholic twin	Paternal nonalc. with MZ alc. co-twin	Paternal nonalc. with DZ alc. co-twin	Both twins nonalc.
Offspring genetic risk	High	High	Moderate	Low
Offspring environmental risk	High	Low	Low	Low

Note: Group 1: all twin fathers with a lifetime diagnosis of alcohol-dependence or abuse regardless of the alcoholism status of his co-twin. Group 2: nonalcoholic fathers with an MZ co-twin having an alcohol-dependence diagnosis. Group 3: nonalcoholic fathers with a DZ co-twin having an alcohol-dependence diagnosis. Group 4: twin-pair fathers have neither alcohol-dependence nor abuse (normal control reference group).

Table 2
Sociodemographic Characteristics for All Subjects by Paternal Alcoholism Status
(Percentages given for dichotomous variables; mean (*SD*) given for continuous variables*)

	Group 1	Group 2	Group 3	Group 4	Entire sample
Family characteristics (as of date of interview)	MZ and DZ AD twins (<i>n</i> = 809)	MZ twin unaffected; co-twin with AD (<i>n</i> = 114)	DZ twin unaffected; co-twin with AD (<i>n</i> = 124)	MZ and DZ unaffected control twins (<i>n</i> = 223)	(<i>n</i> = 1270)
% male offspring	49.3%	54.4%	44.4%	44.4%	48.4%
Child age (yrs)	19.4 (4.1)	19.8 (4.2)	19.0 (3.9)	19.4 (4.0)	19.4 (4.1)
Paternal age (yrs)	50.5 (2.7)	50.8 (2.7)	50.7 (2.4)	51.1 (2.8)	50.7 (2.7)
Maternal age (yrs)	48.0 (5.2)	47.5 (5.1)	48.5 (6.6)	48.5 (3.8)	48.1 (5.0)
% Father employed fulltime	92.7%	91.2%	94.4%	96.0%	93.3%
Father educ. > high school	59.2%	65.8%	71.0%	63.2%	61.7%
Mother educ. > high school	67.0%	54.1%	59.6%	70.0%	66.3%
Marital status: divorced **	20.4%	12.3%	21.0%	13.2%	18.4%
Caucasian race	96.4%	99.1%	91.1%	94.2%	95.7%

Note: * no between group comparisons significant at *p* < .10.
** biological parents of this offspring are divorced.

disorder (provided mother’s influence is controlled), thus confirming the cross-generational, cross-diagnosis transmission of these two disorders reported in the literature. While this contrast is equivalent to any family study (without twins) and does not differentiate between genetic risk or environmental risk, it does establish the significance of father-to-child transmission within this sample that provides the basis for genetically informed discrimination of transmitted influence.

Analyses of group effects to test H2, the common genes hypothesis, are based on the following logic: If common genes are the primary determinant of the phenotypic association between alcoholism and conduct disorder, there should be a similar outcome

risk for the child with an alcoholic father and for the child of a nonalcoholic father whose MZ co-twin is alcoholic (see groups 1 and 2 in Table 1). That is, because MZ twins share 100% of their genes in common, genetic risk should be the same regardless of differences in environment; that is, whether the family environment involves being reared by an alcoholic father or a nonalcoholic (MZ co-twin) father. Thus, the common genes hypothesis would be supported if offspring rates of conduct disorder were similar in groups 1 and 2, and would be refuted if offspring rates of conduct disorder for group 2 were instead similar to normal controls in group 4. It can be seen that group 2 is of particular interest to hypothesis 2 because these

Table 3
Offspring Report of Conduct Disorder Symptoms Across Paternal Alcoholism Status Groups

		Twin-pair alcoholism status				Total	
		Group 1	Group 2	Group 3	Group 4		
		MZ and DZ AD twins	MZ twin unaffected; co-twin with AD	DZ twin unaffected; co-twin with AD	MZ and DZ unaffected control twins		
Number of Sx							
Conduct disorder symptom count	0,1	<i>n</i>	617	89	105	189	1000
		%	76.3%	78.1%	84.7%	84.8%	78.7%
	2	<i>n</i>	64	11	8	16	99
		%	7.9%	9.6%	6.5%	7.2%	7.8%
	3	<i>n</i>	53	5	3	6	67
		%	6.6%	4.4%	2.4%	2.7%	5.3%
	4+	<i>n</i>	75	9	8	12	104
		%	9.3%	7.9%	6.5%	5.4%	8.2%
Totals:		<i>n</i>	809	114	124	223	1270
		%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 4

Odds Ratios (95% confidence intervals) for DSM-IV Conduct Disorder Diagnosis in Offspring as a Function of Family Risk Status and Pertinent Covariates From an Ordinal Logistic Regression

	Offspring conduct disorder
Group 1	
MZ and DZ alcohol abuse/dependent twins	1.81 (1.11–2.96)*
Group 2	
MZ unaffected with alcohol dependent co-twin	1.60 (0.84–3.04)
Group 3	
DZ unaffected with alcohol dependent co-twin	1.04 (0.47–2.32)
paternal illicit drug abuse/dependence	1.29 (0.74–2.24)
paternal psychiatric disorder ¹	0.82 (0.55–1.24)
paternal post-high school education	0.78 (0.55–1.11)
paternal employment	0.50 (0.32–0.80)**
maternal antisocial personality diagnosis	1.42 (0.56–3.60)
maternal alcohol dependence	1.16 (0.64–2.09)
maternal major depression	1.40 (0.90–2.17)
maternal alcohol abuse	0.72 (0.40–1.30)
marital divorce	0.44 (0.29–0.68)***
offspring age 18 and over	1.76 (1.25–2.49)***
male offspring	3.50 (2.48–4.94)***

Note: ¹paternal antisocial personality disorder; conduct disorder; drug abuse; major depression; dysthymia; generalized anxiety, panic and posttraumatic stress disorders.

* $p < .05$; ** $p < .01$; *** $p < .001$

offspring share high genetic risk with offspring in group 1, and share low environmental risk with groups 3 and 4. Therefore, the dominant influence, genes or environment, will be reflected by the relative position of group 2 prevalence between groups 1 and 4, and the two contrasts, groups 1 to 2 and 2 to 4, will test the significance of the respective contributions of these competing influences.

Group 3 provides a test of moderate genetic influence. That is, contrasts of groups 2 to 3 and 3 to 4 test the relative influence of high, medium and low genetic risk in the context of environmental risk that is low and (approximately) equivalent across groups. If group 3 is more similar to groups 1 and 2, moderate genetic factors would be influential; if group 3 is more similar to group 4, moderate genetic factors associated with paternal alcoholism would be shown to be of little consequence to offspring conduct disorder symptom outcomes.

Confirming Design Attributes

The analytic plan included examination of two features of this research design that could potentially influence its validity. In the earlier examination of offspring alcohol use outcomes (Jacob et al., 2003), paternal alcohol dependence and paternal alcohol abuse were similarly predictive of offspring alcohol behaviors. In order to confirm the validity of combining these two

groups in the current study, it was necessary to examine their similarity regarding offspring conduct disorder. The results are presented in the Results section, Confirming Similarity of Alcohol Abuse and Alcohol Dependence Outcomes. Also, given that group 1 is composed of different subgroups of alcoholic fathers, it was necessary to verify the homogeneity of variance across these subgroups to ensure that emergent findings involving group 1 did not result from variation in genetic liability due to differences in the co-twin's risk status within group 1. These results are presented in the Results section, Confirming Homogeneous Genetic Variance in Group 1.

Nested Observations

Family studies and twin studies involve nested subgroups in which individual characteristics may be correlated. Because clustering may violate the assumption of independence of observations required by many statistical procedures, analyses were conducted both without and with adjustments for clustering. Preliminary analyses were conducted using SAS (SAS, 1989); final analyses were conducted using STATA (StataCorp., 2001) including the Huber–White robust variance estimator to adjust for clustering of offspring within families, perhaps the most proximal covariation regarding current analyses. Results were approximately identical to unadjusted findings, and slightly strengthening of current directions of effects.

Results

Sample Characteristics

As shown in Table 2, the four groups of offspring exhibited no significant differences ($p > .10$) for family characteristics. As of the date of interview, twin fathers and mothers averaged 51 and 48 years of age, respectively; over 62% of fathers had more than a high school education; 93% were employed full-time at the time of the study; 18% of the biological parents were divorced; and offspring (48% male) ranged from 12 to 26 years of age. The sample, drawn from records of United States military participation, reflected the racial characteristics of the US armed services which were predominantly of European ancestry.

Group Differences in Offspring Conduct Disorder Outcome

As seen in Table 3, for 2, 3 and 4 conduct disorder symptoms, groups 1 and 2 offspring exhibited elevated prevalence rates compared to offspring in groups 3 and 4; in contrast, for 0 and 1 symptoms, groups 1 and 2 offspring exhibited lower prevalence rates compared to offspring in groups 3 and 4. Aggregating across symptom levels, figure 1 shows dichotomous offspring conduct disorder symptoms (2 or more conduct disorder symptoms vs. 0 to 1 symptoms) according to paternal twin-pair alcoholism group. As seen, both group 1 and 2 have elevated risk compared to group 3 and group 4. This Figure is most illustrative of the pattern emerging

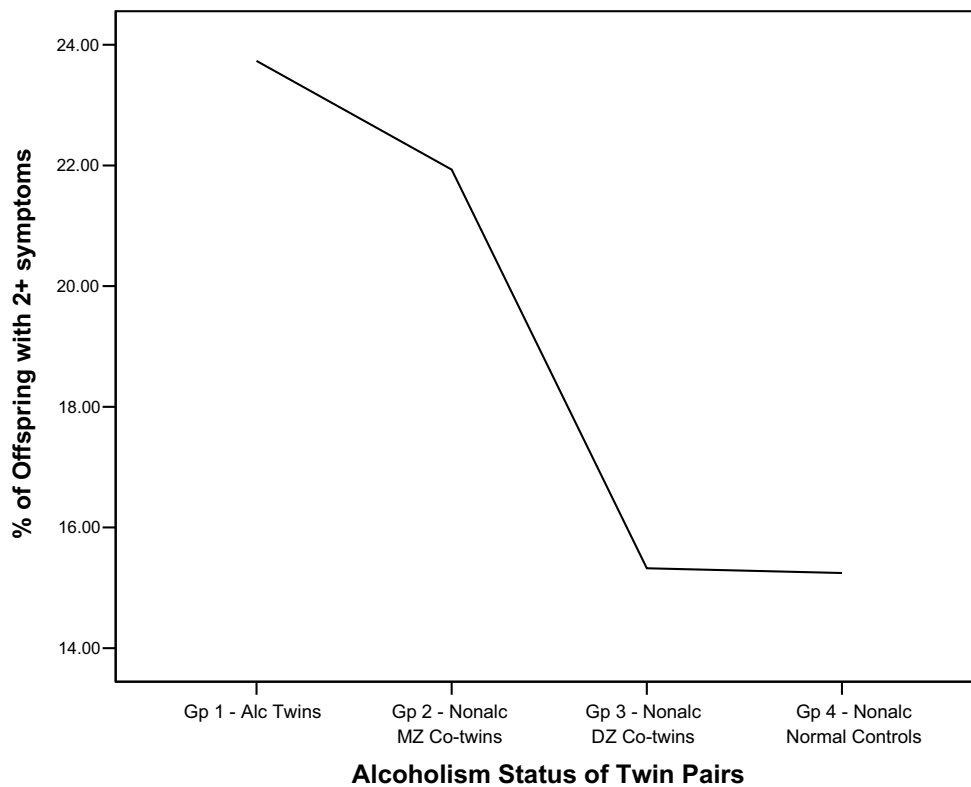


Figure 1

Percent offspring with two or more conduct disorder symptoms by group.

Note elevation of groups 1 and 2.

from analytical findings as described below. (Note, other graphs were consistent with this pattern; for instance, the 3+ graph differed only in being slightly more linear with less ‘knee’ accent).

The results of the ordinal logistic regression analysis are presented in Table 4. All group comparisons are referenced to group 4 (normal controls). Results can be considered in view of levels of genetic and environmental risk shown in Table 1. Concerning group 1, MZ and DZ alcohol abuse/dependent twins, children of alcoholics (group 1) were significantly more likely to exhibit conduct disorder symptoms than were children of nonalcoholics (group 4) after controlling for covariates (odds ratio: 1.81; $p = .02$). Thus, paternal alcoholism (inclusive of genetic and environmental components but adjusted for covariates) significantly predicted offspring conduct disorder.

Concerning group 2, unaffected twins with an alcohol-dependent MZ co-twin, two contrasts were most important, the group 1 to 2 contrast, and the group 2 to 4 contrast. The group 1–2 contrast yielded a nonsignificant group difference (odds ratio: 1.02; $p = .63$), indicating that offspring with high genetic but low environmental risk (group 2) were not different from offspring with both high genetic and high environmental risk (group 1). The group 2–4 contrast, after controlling for paternal and maternal antisocial disorder and other

covariates, indicated a trend toward statistical difference in contrast to normal control offspring (group 4; odds ratio: 1.60; $p = .15$) due to higher rates of conduct disorder symptoms although statistical significance was not achieved. Given the context of competing influences, the evident similarity between group 2 and the elevated offspring conduct disorder rate of group 1 (instead of a similarity between group 2 and the base rate reflecting group 4 normal controls) suggested the prominence of genetic over environmental influences. Given that the group 2 to 4 contrast did not reach significant difference, this finding suggests (but does not conclude) that genetic influences are the primary determinants of offspring outcome.

Group 3 examined the results of moderate genetic risk given low environmental risk (environmental risk was equivalent and low across groups 2, 3 and 4). As illustrated in Figure 1, offspring of a nonalcoholic twin with a DZ co-twin who was alcoholic (group 3) did not exhibit elevated conduct disorder rates compared with offspring of nonalcoholic control fathers (group 4; odds ratio: 1.04; $p = .92$). Thus, moderate genetic risk (group 3) did not differentiate these offspring from normal control offspring. This was in contrast to high genetic risk (group 1) which did differentiate offspring from normal controls.

In addition to outcome differences related to alcohol risk status, several covariates were significantly related to offspring outcomes even after controlling for alcohol risk and other covariates: age of offspring ($p = .0002$); gender of offspring ($p = .0001$); father's employment status ($p = .004$); and divorce status of the parents ($p = .0002$). These are known risk factors for offspring conduct disorder. In the case of divorce, however, the direction of the effect is counterintuitive, that is, divorce appears to lower the risk of conduct disorder. This could be a simple anomaly or an artifact of the removal of parental antisocial personality disorder variance (given that antisocial personality disorder notably contributes to marital dissolution). Paternal educational level, paternal psychiatric comorbidity, and maternal alcohol and psychiatric comorbidity were not significantly related to outcome.

Confirming Design Attributes

To strengthen interpretability of the above findings, analyses were undertaken to confirm the validity of two design features.

Confirming Similarity of Alcohol Abuse and Alcohol Dependence Outcomes

Our previous finding that paternal history of alcohol dependence (AD) and paternal history of alcohol abuse (AB) were similarly predictive of offspring alcohol behaviors (Jacob et al., 2003) suggested that twins with AB history could be grouped with AD twins in the current analysis. Nevertheless, it was necessary to confirm this AD-AB similarity when considering offspring conduct disorder as the outcome of interest. Therefore, AB and AD twins were reclassified to distinguish paternal alcohol abuse from paternal alcohol dependence for both MZ and DZ pairs. Six groups were formed: group 1 — all AD twin fathers regardless of co-twin status; group 2 — AB fathers with alcohol-dependent MZ co-twins; group 3 — nonalcoholic fathers with AD MZ co-twins; group 4 — AB fathers with AD DZ co-twins; group 5 — nonalcoholic fathers with AD DZ co-twins; group 6 — nonalcoholic twin pairs as a reference group (any control pair currently found to meet diagnostic criteria for AB or AD was deleted). As expected, offspring in both group 1 and group 2 exhibited elevated rates of conduct disorder symptoms compared to the offspring in group 6 (odds ratios = 6.5 and 2.8 respectively; $p = .01$ and $.09$) whereas all other contrasts with group 6 were non-significant. These findings support the combining of group 1 and group 2 into a single category within the current four-group design.

Confirming Homogeneous Genetic Variance in Group 1

To ensure that emergent findings involving group 1 were not dependent on variation in genetic liability arising from differences in the co-twin's risk status within group 1, another examination of subgroup differences was undertaken. These subgroups of group 1

alcoholic fathers were based upon each co-twin's alcoholism status (AD, AB or unaffected) and zygosity (MZ and DZ pairs). Here, all twins were AD whereas co-twin status was: (1) alcohol-dependent MZ co-twins; (2) alcohol-abusing MZ co-twins; (3) nonaffected MZ co-twins; (4) alcohol-dependent DZ co-twins; (5) alcohol-abusing DZ co-twins; and (6) nonaffected DZ co-twins. Although each subgroup represented potentially different influences on child outcome arising from differential genetic loading across the subgroups, results confirmed the homogeneity of odds ratios for group 1 across co-twin zygosity (MZ, DZ) and across co-twin history of alcohol use (AD, AB, unaffected). These results suggest that offspring with an alcohol-dependent father whose co-twin is nonabusing and nondependent is at no less genetic risk than the child of a dependent father whose co-twin is abusing or dependent. The absence of heterogeneity in offspring outcome as related to the co-twin's alcohol status supported the decision to include all families with an alcoholic father as a single predictive category, group 1.

Discussion

Current findings provide additional evidence for the contention that alcoholism and conduct disorder both arise, to a significant degree, from common genetic factors. Specifically, findings indicated that (1) paternal alcoholism predicted subsequent offspring conduct disorder in the same way that it predicted offspring alcoholism; and (2) paternal alcoholism, to a large extent, predicted offspring conduct disorder even when family environmental risk was minimized, thus suggesting that genetic mechanisms underlie the observed effects.

Concerning hypothesis 1, results clearly indicated that the offspring of alcohol-dependent fathers (group 1) were significantly more likely to have elevated rates of conduct disorder symptoms than were offspring of normal control fathers (group 4). Thus, when considering these two phenotypes, the nonindependence of alcoholism and conduct disorder was evident. One implication is that parent-to-child transmission of liability may be less specific than diagnostic categories imply given that the transmission of a common liability can impact different classes of disorder, that is, substance-use disorders and child psychiatric disorders.

Concerning hypothesis 2, analyses examined whether genes alone could account for this effect, thus supporting the common genes hypothesis, or whether some combination of genetic and environmental factors were involved. Results were considered in the context of competing influences. Prevalence rates for offspring conduct disorder symptoms indicated a close similarity between group 2 and the elevated rate of offspring conduct disorder symptoms in group 1 (as well as the consequent absence of similarity between group 2 and the offspring conduct

disorder base rate in group 4, normal controls). The implication is that genetic factors were much more important to the determination of offspring conduct disorder symptom outcomes than environmental factors. While prevalence rates suggested genetic influences, and little evidence supported environmental influences, statistical significance was not definitive. Specifically, in support of groups 1–2 similarity was a nonsignificant group 1 to 2 contrast ($p = .63$). However, the dissimilarity between group 2 and group 4 only approached significance ($p = .15$), and thus was less than conclusive in differentiating group 2 elevations from normal control base rates (group 4). Hence, a certain ambiguity remained in interpretation of these results. Several considerations were examined in an effort to identify the most parsimonious explanation of current findings.

First, it was clear that little or no evidence supported an environmental interpretation. That is, if environmental effects were primary, their removal should have resulted in a substantial lowering of risk for offspring conduct disorder symptoms; this did not occur. Instead, risk for group 2 offspring remained substantially elevated. Second, findings indicated an elevation of group 2 offspring conduct disorder symptom rates approximating those of group 1 levels which was, at the least, suggestive of the influence of a high level of genetic risk present in group 2 offspring. On the other hand, the lack of statistical significance of the group 2 to 4 contrast required resolution.

The most parsimonious interpretation of these findings is that genetic factors and, to a lesser degree, environmental factors both were at play in these effects. That is, although there is no evidence for a substantial environmental influence in these results, the above findings could be explained as the consequence of a small environmental effect interacting with a prominent genetic effect. Specifically, the environmental effect would result in a reduction of the size of group 2 to 4 contrast and its significance estimate, and would produce the above pattern of results.¹

It appears likely that greater statistical power would have produced a more conclusive genetic finding. If true, it should be remembered that, in addition to other limiting factors (see Limitations), we used an intentionally conservative design by treating parental ASP/CD, other psychopathology and other demographics as covariates in order to reduce ambiguity in interpretation of these results. These design judgments also lowered power. As such, it may be that the significance test of the group 2 to 4 contrast is a 'lower-bound' estimate of the true effect.

In summary, the 'common genes' hypothesis would be supported if the offspring of nonalcoholic twins (low environmental risk) who had an alcohol dependent MZ co-twin (high genetic risk) exhibited elevated rates of conduct disorder symptoms (see Hypothesis 2). In fact, the prevalence rates were elevated in the current sample of offspring of nonalcoholics (group 2)

and approximated the elevations of the offspring of alcoholics group. This elevation appeared to occur in the absence of environmental risk, that is, among offspring who were not raised by an alcoholic father. Therefore, current findings lead to the conclusion that environmental influences were a minimal effect in group 2, but that they appeared to be present sufficiently to result in a minor decrease in the effect size of an otherwise unambiguous genetic effect. Therefore, it seems reasonable to conclude that the genes associated with parental alcoholism were responsible for the observed elevation in offspring conduct disorder symptom rates. To the extent that this is true, the common genes hypothesis is supported.

In an effort to strengthen interpretation of observed effects, we examined other offspring diagnoses including depression, generalized anxiety disorder, agoraphobia, social phobia, attention-deficit/hyperactivity disorder, oppositional-defiant disorder, and marijuana and nicotine dependence. No pattern of findings across groups emerged with sufficient clarity so as to be interpretable as evidence for common genetic influences. However, these were preliminary tests and were limited by several factors: (a) some diagnoses had small n s; (b) this is a high-risk alcoholism sample which may not be representative of internalizing disorders; and (c) more extensive analyses would be required to provide an adequate basis for interpreting these results. Nevertheless, drawing from the current study and our previous effort, it appears clear that offspring alcohol abuse/dependence and offspring conduct disorder are clearly associated with paternal alcoholism through a genetic mechanism.

Limitations

Consideration of limitations is important in the interpretation of present findings. For instance, examination of the etiology of conduct disorder is limited by the low prevalence of this disorder in the general population and by the difficulty in obtaining sufficient sample size and statistical power when a sample is not selected to be high risk for conduct disorder. As well, statistical power was limited in this particular COT model due to its dependence on twins who are discordant for alcoholism, and by the desire to account for many potential confounds (D'Onofrio et al., 2003). Further, since the study sample was largely composed of intact marriages with children, more extreme forms of alcoholism, antisocial behavior, and family disruption may have been lost through divorce and/or refusal (very disturbed families participate less often in family studies) thus reducing the variability due to negative environmental influences. Finally, all designs are associated with certain assumptions and limitations. In general, the COT design is more powerful for detecting environmental rather than genetic effects (Heath & Eaves, 1985); even though it was important as an alternative methodology in the current study, this application may not have

been its strongest application. Other general limitations of the COT design include the inability to identify reciprocal environmental influences, reliance on the equal environments assumption (EEA, Xian et al., 2000), and on comparable treatment of twins and singletons (Rutter et al., 2001). Most evidence to date has supported these assumptions. (For a critical review of genetic designs and their limitations, see Rutter [2001], and for the COT design, see Heath & Eaves [1985] and Silberg & Eaves [2004]).

The current study contributes to a growing body of evidence addressing the proposition that there are two primary dimensions of psychopathology, an externalizing and an internalizing dimension, each having a sizeable genetic component. The various disorders that are subsumed under each broad band factor appear to share common genetic variance which accounts, in part, for observed patterns of comorbidity within these dimensions and for transmission characteristics across generations. As summarized by Widiger and Clark (2000), and most recently demonstrated by Kendler et al. (2003), these two genetically influenced factors may be two cornerstone dimensions central to our understanding and classification of psychiatric disorders. The current study supports the notion of common genes underlying at least two disorders in the externalizing dimension, alcoholism and conduct disorder. Use of alternative methodologies, such as the COT design, contributes a unique perspective in efforts aimed at elucidating these relationships.

Acknowledgments

This study was supported by grants AA11667 and AA11822 and center grant AA11998 from the National Institute on Alcohol Abuse and Alcoholism and by a Merit Review Grant from the Department of Veterans Affairs Medical Research Service, Washington, DC (Dr Jacob).

The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. Numerous organizations have provided invaluable assistance in the conduct of this study, including: Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.

Endnote

1 The psychosocial literature and, to a lesser extent, the behavioral genetic literature both indicate a role for environmental influences in these effects. For instance, Krueger et al. (2002) found that after accounting for a

latent broadband externalizing factor, shared environmental influences remained, accounting for 26% of the outcome variance associated specifically with conduct disorder diagnoses. In this case, shared environmental influences appeared to play a greater role in the development of conduct disorder than in alcoholism and other externalizing disorders. As well, our earlier study of offspring alcoholism (Jacob et al., 2003) reported that offspring alcohol abuse/dependence was significantly elevated in families with an alcoholic father (compared to normal controls) whereas symptoms were less elevated in the nonalcoholic, high genetic risk families, thus suggesting a gene \times environment (G \times E) interaction. Therefore, it seems plausible that environmental influences were present and made some contribution to the above effects in the manner described.

References

- American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Bouchard, T. (2003). The mystery of culture. *Science*, 298, 2325.
- Brant, R. (1990). Assessing proportionality in the proportional odds model for ordinal logistic regression. *Biometrics*, 46, 1171–1178.
- Bucholz, K. K., Cloninger, C. R., Dinwiddie, S. H., Hesselbrock, V. M., Nurnberger, J. I., Reich, T., Schmidt, I., & Schuckit, M. A. (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: A report of the reliability of the SSAGA. *Journal of Studies on Alcohol*, 55, 149–158.
- Caspi, A., Moffitt, T., Newman, D., & Silva, P. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders. *Archives of General Psychiatry*, 53, 1033–1039.
- Derogatis, L., Lipman, R., Rickels, K., Uhlenhuth, E., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behavioral Science*, 19, 1–19.
- D'Onofrio, B. M., Turkheimer, E. N., Eaves, L. J., Corey, L. A., Berg, D., Solaas, M. H., & Emery, R. E. (2003). The role of the children of twins design in elucidating causal relations between parent characteristics and child outcomes. *Journal of Child Psychology, Psychiatry, and Allied Disciplines*, 44, 1130–1145.
- Eisen, S., True, W., Goldberg, J., Henderson, W., & Robinette, C. D. (1987). The Vietnam Era Twin (VET) Registry: Method of construction. *Acta Geneticae Medicae et Gemellologiae*, 36, 61–67.
- Eisen, S. A., Goldberg, J., True, W. R., & Henderson, W. R. (1991). A co-twin control study of the effects of the

- Vietnam War on the current physical health of veterans. *American Journal of Epidemiology*, 134, 49–58.
- Heath, A. C., Bucholz, K. K., Madden, P. A. F., Dinwiddie, S. H., Slutske, W. S., Statham, D. J., Dunne, M. P., Whitfield, J. B., & Martin, N. G. (1997). Genetic and environmental contributions to alcohol dependence risk in a national twin sample: Consistency of findings in women and men. *Psychological Medicine*, 27, 1381–1396.
- Heath, A. C., & Eaves, L. J. (1985). Resolving the effects of phenotype and social background on mate selection. *Behavior Genetics*, 15, 15–30.
- Helzer, J. E., & Pryzbeck, T. R. (1988). The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. *Journal of Studies on Alcohol*, 49, 219–224.
- Henderson, W. G., Eisen, S., Goldberg, J., True, W., Barnes, J. E., & Vitek, M. E. (1990). The Vietnam Era Twin Registry: A resource for medical research. *Public Health Report*, 105, 368–373.
- Jacob, T., Waterman, B., Heath, A., True, W., Bucholz, K. K., Haber, R., Scherrer, J., & Fu, Q. (2003). Genetic and environmental influences on offspring alcoholism: New insights using a children-of-twins design. *Archives of General Psychiatry*, 60, 1265–1272.
- Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*, 60, 929–937.
- Krueger, R. F., Hicks, B. M., Patrick, C. J., Carlson, S. R., Iacono, W. G., & McGue, M. (2002). Etiologic connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology*, 111, 411–424.
- Loukas, A., Piejak, L. A., Bingham, C. R., Fitzgerald, H. E., & Zucker, R. A. (2001). Parental distress as a mediator of problem behaviors in sons of alcohol-involved families. *Family Relations*, 50, 293–301.
- Lynskey, M. T., Fergusson, D. M., & Horwood, L. J. (1994). The effect of parental alcohol problems on rates of adolescent psychiatric disorders. *Addiction*, 89, 1277–1286.
- McGue, M. (1997). A behavioral-genetic perspective on children of alcoholics. *Alcohol Health and Research World*, 21, 210–217.
- Nance, W. E., & Corey, L. A. (1976). Genetic models for the analysis of data from the families of identical twins. *Genetics*, 83, 811–826.
- Plomin, R. E., & Hershberger, S. (1991). Genotype-environment interaction. In T. D. Wachs & R. Robert (Ed.), *Conceptualization and measurement of organism-environment interaction* (vol. xii, pp. 29–43). Washington, DC: American Psychological Association.
- Rutter, M., Pickles, A., Murray, R., & Eaves, L. J. (2001). Testing hypotheses on specific environmental causal effects on behavior. *Psychological Bulletin*, 127, 291–324.
- SAS Institute, Inc. (1989). *SAS/STAT user's guide* (Version 6, 4th ed.). Cary, NC: Author.
- Scherrer, J. E., Waterman, B. M., Heath, A. C., Bucholz, K. K., True, W. R., & Jacob, T. (2004). Are substance use, abuse and dependence associated with study participation? Predictors of offspring nonparticipation in a twin-family study. *Journal of Studies on Alcohol*, 65, 140–144.
- Sher, K. J., Walitzer, K. S., Wood, P. K., & Brent, E. E. (1991). Characteristics of children of alcoholics: Putative risk factors, substance use and abuse, and psychopathology. *Journal of Abnormal Psychology*, 100, 427–449.
- Silberg, J. L., & Eaves, L. J. (2004). Analysing the contributions of genes and parent-child interaction to childhood behavioural and emotional problems: A model for the children of twins. *Psychological Medicine*, 34, 347–356.
- Skinner, H., & Schuller, R. (1982). *Validation of the lifetime drinking history: Biochemical, medical history and psychosocial evidence*. Unpublished manuscript. Addiction Research Foundation at Toronto, Canada.
- Slutske, W. S., Heath, A. C., Dinwiddie, S. H., Madden, P. A. F., & Bucholz, K. K. (1998). Common genetic risk factors for conduct disorder and alcohol dependence. *Journal of Abnormal Psychology*, 107, 363–374.
- Slutske, W. S., Heath, A. C., Madden, P. A. F., Bucholz, K. K., Statham, D. J., & Martin, N. G. (2002). Personality and the genetic risk for alcohol dependence. *Journal of Abnormal Psychology*, 111, 124–133.
- StataCorp. (2001). *Stata 7: Stata user's guide* (Release 7). College Station, TX: Stata Press.
- Stewart, M., deBlois, S., & Cummings, C. (1980). Psychiatric disorder in the parents of hyperactive boys and those with conduct disorder. *Journal of Child Psychology, Psychiatry, and Allied Disciplines*, 21, 283–292.
- Tarter, R. E., & Vanyukov, M. (1994). Alcoholism: A developmental disorder. *Journal of Consulting and Clinical Psychology*, 62, 1096–1107.
- Tsuang, M. T., Lyons, M. J., Eisen, S. A., Goldberg, J., True, W., Lin, N., Meyer, J. M., Toomey, R., Faraone, S. V., & Eaves, L. (1996). Genetic influences on DSM-III-R drug abuse and dependence drugs: A study of 3,372 twin pairs. *American Journal of Medical Genetics*, 67, 473–477.
- West, M., & Prinz, R. (1987). Parental alcoholism and childhood psychopathology. *Psychological Bulletin*, 102, 204–218.
- Widiger, T. A., & Clark, L. A. (2000). Toward DSM-V and the classification of psychopathology. *Psychological Bulletin*, 126, 946–963.

- Windle, M. (1997). A critical analysis of COA research: A panel discussion. *Alcohol Health and Research World*, 21, 258–265.
- Windle, M., & Searles, J. (Eds.). (1990). *Children of alcoholics: Critical perspectives*. New York: Guilford Press.
- Windle, M., & Windle, R. C. (1993). The continuity of behavioral expression among disinhibited and inhibited childhood subtypes. *Clinical Psychology Review*, 13, 741–761.
- Xian, H., Scherrer, J. F., Eisen, S. A., True, W. R., Heath, A. C., Goldberg, J., Lyons, M. J., & Tsuang, M. T. (2000). Self-reported zygosity and the equal-environments assumption for psychiatric disorders in the Vietnam Era Twin Registry. *Behavior Genetics*, 30, 303–310.
- Zucker, R. A. (1994). Pathways to alcohol problems and alcoholism: A developmental account of the evidence for multiple alcoholisms and for contextual contributions to risk. In R. Zucker & J. Howard (Eds.), *Research Monograph – 26. The development of alcohol problems: Exploring the biopsychosocial matrix of risk* (pp. 255–290). Washington, DC: US Department of Health and Human Services.
- Zucker, R. A. (Ed.). (2002). *Causal structure of alcohol use and problems in early life: Multilevel etiology and implications for prevention*. Chicago, IL: Child Welfare League of America.
- Zucker, R. A., Fitzgerald, H. E., & Moses, H. D. (1995). Emergence of alcohol problems and the several alcoholisms: A developmental perspective on etiologic theory and life course trajectory. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology. Volume 2: Risk, disorder, and adaptation*. New York: Wiley.
-