

## Behavioral disinhibition and the development of substance-use disorders: Findings from the Minnesota Twin Family Study

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### Abstract

One variant of substance-use disorder is characterized by behavioral disinhibition. In this report, we marshal evidence for a model for the development of this variant. We hypothesize that genetic liability for this variant is reflected in a spectrum of risk indicators linked to the inability or unwillingness to inhibit behavioral impulses. Included in this spectrum are personality traits suggesting low constraint, and externalizing psychopathology, including conduct, oppositional defiant, and attention-deficit disorder in children and antisocial personality disorder and behavior in adults. We further hypothesize that these individual differences in behavioral disinhibition are manifestations of underlying central nervous system processes associated with various psychophysiological anomalies, some of which may index genetic risk for substance abuse. Support for the model is derived from the analysis of findings from the Minnesota Twin Family Study, an epidemiological investigation of approximately 2,700 adolescent twins and their parents.

Substance use disorders are among the most strongly familial of the mental disorders. The children of alcoholics are some 4–5 times more likely to develop alcoholism than the children of nonalcoholics (Cotton, 1979), and the rate of substance abuse among the biological relatives of individuals with cocaine (Luthar & Rounsaville, 1993) and opioid (Kosten, Rounsaville, Kosten, & Merikangas, 1991) dependence is substantially elevated over population base rates. Significantly, there appears to be generalized familial transmission of substance abuse risk. For example, the rates of alcohol and nicotine dependence are both elevated among the biological relatives of cannabis abusers (Merikangas et al.,

1998), and, conversely, the rates of alcohol dependence, marijuana dependence, and smoking are all elevated among the biological relatives of alcoholics (Bierut et al., 1998).

Understanding the mechanisms that underlie the familial transmission of substance use disorders is further complicated by the clinical heterogeneity of these disorders. There is substantial comorbidity, not only among the different substance use disorders but also between substance use disorders and other mental disorders (Kessler et al., 1997). Alcohol researchers have attempted to clarify this clinical heterogeneity through the development of typological models. In 60 years of efforts to identify subtypes of alcoholism (e.g., Knight, 1938), one distinction has consistently emerged: that between an early-onset form that is associated with polysubstance abuse, and other antisocial behavior, and a late-onset form with little evidence of antisocial behavior. The subtypes of alcoholism identified in the recent cluster analytic study by Babor et

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The research described in this report was supported by NIH Grants DA 05147, AA09367, AA00175, and MH 17069.

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al. (1992) serve to illustrate the distinction. The first subtype, designated in that study as Type A, was characterized by later age at onset, fewer childhood risk factors such as hyperactivity or conduct disorder, less severe dependence, fewer alcohol-related problems, less treatment for alcoholism, and less psychopathology. The second subtype, Type B, was characterized by early age at onset, relatively high rates of childhood conduct disorder and hyperactivity, more severe dependence, more treatment, and more psychopathology. Importantly, this distinction does not appear to be alcoholism specific, as cocaine abusers can also be subclassified into a more and less antisocial type (Ball, Carroll, Babor, & Rounsaville, 1995).

In this article we describe a program of research aimed at understanding the familial transmission of substance abuse (SA) from a developmental, behavioral genetic perspective. Although this project, known as the Minnesota Twin Family Study (MTFS), has multiple aims, we focus here on describing the nature and familial transmission of an early-onset, antisocial form of SA. Specifically, we propose that this form of SA is highly heritable and characterized by personality traits, behavioral disorders, and psychophysiological indicators that reflect a general disposition towards behavioral disinhibition (Iacono, 1998; Iacono, Lykken, & McGue, 1996). Three major classes of individual-level risk factors are hypothesized to mediate the inheritance of this form of SA: (a) psychiatric disorders (Brooner, King, Kidorf, Schmidt, & Bigelow, 1997; Clark et al., 1997), (b) personality characteristics (Sher & Trull, 1994; Tarter, 1988), and (c) psychophysiological markers (Iacono, 1998).

We review evidence for this hypothesis first by examining various independent investigations showing that these risk classes (a) are strongly interrelated; (b) associated with a family history of alcoholism, SA, and behavioral disinhibition; and (c) are substantially heritable. We then describe the MTFS, providing an overview of its rationale and methodology, especially as it pertains to the evaluation of this hypothesis. Although the extant literature offers tentative support for the hy-

pothesis, there is no single study that comprehensively evaluates its many components. The MTFS represents an effort to accomplish this objective using a population-based sample that is broadly representative of Minnesota families. Among our goals is that of providing insights into how genes and environment interact to influence the development of undersocialized behavior leading to SA. Following our overview of the MTFS, we present findings from the MTFS that support the hypothesis and extend the existing literature by illustrating that these various manifestations of behavioral disinhibition reflect shared genetic effects associated with psychophysiological anomalies leading to the development of SA.

#### **Undersocialized Children, Especially Children of Alcoholics, Are at Risk for Early-Onset SA**

A spectrum of externalizing psychopathology, emerging during childhood and adolescence and transmitted in alcoholic families, appears to be related to the development of an undersocialized form of SA. This spectrum includes disorders such as attention-deficit-hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD). Evidence relating these early forms of undersocialized behavior to the later development of alcoholism and other forms of SA comes from several sources. First, retrospective classifications of alcoholism (e.g., Babor et al., 1992) have found that alcoholics with an early age of onset of alcohol problems are especially likely to have exhibited childhood CD and adult antisocial behavior (AAB). In addition, prospective studies indicate that conduct problems and impulsivity often precede the development of alcohol and drug problems (see review by Hawkins, Catalano, & Miller, 1992) and that early conduct problems increase risk for later substance problems (Windle, 1990), including drug abuse (Brook, Cohen, Whiteman, & Gordon, 1992). Finally, reviewers of the literature on children of alcoholics (COAs) have noted that COAs tend to show more externalizing behaviors, such as hyperactivity, and a greater propensity for an-

tisocial behaviors when compared to non-COAs (e.g., Sher, 1991).

Recent longitudinal research further establishes that the familial transmission of SA is associated with externalizing behavioral problems that emerge early in life (typically prior to substance use initiation), persist developmentally, and are predictive of early-onset SA. Thus, Carbonneau et al. (1998) found that 6-year-old sons of alcoholic fathers were more physically aggressive, oppositional, and hyperactive than sons of nonalcoholic fathers; Chassin, Rogosch, and Barrera (1991) found that adolescent offspring of male alcoholics were at elevated risk for internalizing and externalizing symptoms, which subsequently predicted increased rates of substance use disorders in adulthood (Chassin, Pitts, DeLucia, & Todd, 1999); and Sher, Walitzer, Wood, and Brent (1991) found that young adult COAs reported more alcohol and drug problems and higher levels of behavioral undercontrol and neuroticism than adult children of nonalcoholics.

Despite the consistency of these findings, it is important to recognize that many COAs do not manifest behavioral or substance use problems (e.g., West & Prinz, 1987). The clinical heterogeneity of parental alcoholism is likely to account, in part, for the heterogeneous outcomes seen among COAs. For example, in a prospective study of preschool children, Zucker, Ellis, Bingham, and Fitzgerald (1996) found that children of "antisocial alcoholics" differed from children in nonantisocial families (both alcoholic and control) on a number of risk factors, including temperament, externalizing behavior problems, and hyperactivity, and these "subtype" differences in behavior were sustained into middle childhood.

#### **Personality Is Associated With Disinhibitory Psychopathology and SA**

In addition to externalizing psychopathology, certain personality factors are associated with alcoholism and SA in general and the under-socialized form of these disorders in particular. Two dimensions of personality have been consistently associated with alcoholism: nega-

tive emotionality (the tendency to experience negative mood states or distress) and behavioral disinhibition (i.e., high novelty seeking, impulsivity, lack of constraint; Sher & Trull, 1994). The latter dimension appears to be specifically associated with the antisocial form of alcoholism. For example, in a recent review of studies using Cloninger's Tridimensional Personality Questionnaire (TPQ), Howard, Kivlahan, and Walker (1997) concluded that the TPQ Novelty-Seeking scale (an indicator of behavioral disinhibition) (a) consistently predicts early onset alcohol abuse and criminality and (b) discriminates alcoholics exhibiting antisocial behavior from alcoholics who do not. Studies using inventories other than the TPQ also confirm that indicators of behavioral disinhibition differentiate antisocial and nonantisocial alcoholics (e.g., Holdcraft, Iacono, & McGue, 1998).

Longitudinal studies confirm that personality differences between alcoholics and nonalcoholics predate the onset of SA and are predictive of other forms of disinhibitory psychopathology. For example, high novelty seeking predicts early onset of substance use in adolescence (Masse & Tremblay, 1997) and early onset SA in adulthood (Cloninger, Sigvardsson, & Bohman, 1988). Similar personality factors have been implicated in early-onset delinquency as well (Tremblay, Pihl, Vitaro, & Dobkin, 1994). Remarkably these predictive relationships begin to emerge as early as the toddler years. Caspi, Moffitt, Newman, and Silva (1996) reported that children identified as undercontrolled (i.e., impulsive, restless, and distractible) at age 3 years were especially likely, at age 21 years, to have ASPD, to be involved in crime (conviction records), and to have alcohol problems.

#### **Genes Influence Alcoholism, SA, and Associated Indicators of Disinhibitory Psychopathology and Behavior**

Twin studies of alcoholism in men have consistently reported higher monozygotic (MZ) than dizygotic (DZ) twin concordance, and adoption studies have consistently reported elevated rates of alcoholism among the reared-away sons of alcoholic fathers compared to

the reared-away sons of nonalcoholics (McGue, 1999). Moreover, although early twin and adoption studies suggested little genetic influence on alcoholism risk in women, these studies typically involved modest-sized samples and may have thus lacked statistical power. More recent twin studies involving larger samples have reported genetic effects on alcoholism risk in women that are comparable to the effects observed in men (Heath et al., 1997; Kendler, Heath, Neale, Kessler, & Eaves, 1992).

Genetic factors may, however, contribute differentially to alternative forms of alcoholism. Cloninger (1987) posited the existence of two etiologically distinct forms of alcoholism, having different genetic, personality, and neurobiological bases. These two types of alcoholism (designated Type I and II by Cloninger) correspond roughly to the nonantisocial and antisocial forms of alcoholism noted earlier. Based on an analysis of the Stockholm Adoption Study, Cloninger, Bohman, and Sigvardsson (1981) concluded that the antisocial, Type II form of alcoholism was much more heritable than the nonantisocial, Type I form (heritability,  $h^2$ , estimates of .90 and less than .40, respectively). Importantly, key findings from the Stockholm Adoption Study were independently replicated in a second Swedish city (Sigvardsson, Bohman, & Cloninger, 1996). More recently, genetic linkage was reported between alcoholism associated with antisociality and a serotonin receptor gene associated with aggression and impulsivity (Lappalainen et al., 1998).

Although the behavioral genetic literature on substance use disorders other than alcoholism is limited, these studies consistently implicate the importance of genetic factors in these disorders. In a recent review of behavioral genetic research on smoking, Heath and Madden (1995) concluded that the heritability of current smoking (estimates ranging from approximately 50 to 60%) was similar in magnitude to the heritability of alcoholism risk. In contrast, behavioral genetic studies of illicit substance abuse suggest that genetic influences, although significant, may be less salient than for the abuse of licit substances like nicotine and alcohol. For example, Pickens et

al. (1991) reported heritability estimates of 31% in men and 22% in women, and Tsuang et al. (1996) reported a heritability estimate of 34% in twin studies of drug use disorder (other than alcohol or tobacco).

In addition to substance use disorders, behavioral genetic research also supports a substantial genetic contribution to many of the dimensions related to behavioral disinhibition, such as various forms of childhood externalizing psychopathology (i.e., ADHD, CD and ODD), antisocial behavior, and the personality dimension of constraint. Evidence from twin studies suggests that 66–80% of individual differences in ADHD symptoms and dimensions and 40–70% of individual differences in CD are associated with genetic factors (Eaves et al., 1997; for an exception, see Lyons et al., 1995; Nadder, Silberg, Eaves, Maes, & Meyer, 1998; Sherman, Iacono, & McGue, 1997; Sherman, McGue, & Iacono, 1997; Silberg et al., 1996; Slutske et al., 1997). Although the number of behavioral genetic studies of ODD lags behind that of ADHD and CD, two twin study reports suggest that 40–75% of the variance in ODD is associated with additive genetic factors (Eaves et al., 1997; Nadder et al., 1998). Moreover, the relevant behavioral genetic literature (e.g., van den Bree, Svikis, & Pickens, 1998) indicates that there is a substantial genetic influence on individual differences in adult antisocial behavior and criminality, and the heritability of constraint has been estimated to be on the order of 50% in several recent twin studies (Billig, Hershberger, Iacono, & McGue, 1996; Finkel & McGue, 1997; Tellegen et al., 1988). The genetic factors influencing each of the various indicators of disinhibitory behavior and SA appear to overlap substantially. For example, twin studies suggest that approximately 50% of the covariance between ADHD and CD/ODD owes to genetic factors shared by the disorders (Nadder et al., 1998; Silberg et al., 1996), a finding that is further supported by the common association of ADHD, CD, and ODD with genetic polymorphisms affecting dopaminergic neurotransmission (Comings et al., 1996; Cook et al., 1995). Moreover, both adoption (Bohman, Cloninger, Sigvardsson, &

von Knorring, 1982; Cloninger, Bohman, Sigvardsson, & von Knorring, 1985) and twin studies (Slutske et al., 1998) indicate a substantial genetic overlap between alcoholism and indicators of antisocial behavior (i.e., CD and criminality).

### **Psychophysiological Measures Are Associated With Behavioral Disinhibition and Genetic Risk for SA**

Support for the role of behavioral disinhibition in the pathogenesis of an antisocial form of SA comes from psychophysiological research on genetically influenced measures that appear to index both individual differences in disinhibited psychopathology and risk for developing substance use disorders. The most consistent set of findings in this area involves extreme responses in both the autonomic (e.g., heart rate and skin conductance) and the central nervous system (e.g., P3 amplitude).

#### *Autonomic hypoactivity*

Children and adolescents at risk for developing antisocial or aggressive behavior appear to have relatively low skin conductance and heart rate orienting responses, and poor classical conditioning of these responses (see Raine, 1996, for a review). Resting heart rate has also been found to be lower in boys formally diagnosed with CD (Lahey, Hart, Pliszka, Applegate, & McBurnett, 1993), ODD (van Goozen et al., 1998), and smaller skin conductance orienting responses have been found in boys with CD (Schmidt, Solant, & Bridger, 1985) and children with ADHD (Iaboni, Douglas, & Ditto, 1997; but see Pliszka, Hatch, Borchering, & Rogeness, 1993; Shibaiki, Yamanaka, & Furuya, 1993). Importantly, these autonomic measures when assessed in early childhood are predictive of the emergence of antisocial behavior in early adolescence (Raine, Venables, & Mednick, 1997) and criminality in late adolescence and early adulthood (Raine, Venables, & Williams, 1990, 1995).

Fowles (1980), adapting Gray's (1975) model, suggested that a relatively weak moti-

vational system (the Behavioral Inhibition System or BIS) sensitive to conditioned cues of punishment or frustrative nonreward may underlie both the development of primary psychopathy and skin conductance hyporesponsivity. Threatening stimuli do not evoke the same degree of arousal in those with a weak BIS, and thus skin conductance measures of arousal, as well as passive avoidance learning, are reduced.

Based on Fowles's model, we would predict that individuals with SA or a family history of SA (and in particular the antisocial form of SA) would be characterized by a weak BIS. Consistent with this expectation, Finn, Kessler, and Hussong (1994) have reported evidence of reduced functioning of an inhibitory control system like the BIS in non-alcoholic men with a multigenerational family history of alcoholism. When compared to nonalcoholic men from families with a low density of alcoholism, these relatives of alcoholics showed poor discrimination in their skin conductance responses between stimuli paired with shock and other, unpaired stimuli, indicating poor classical conditioning to signals predicting aversive consequences. Nonetheless, hyporesponsivity to noxious stimuli is not always observed among those with a family history of alcoholism (e.g., Finn, Zeitouni, & Pihl, 1990), perhaps because the proportion of undersocialized alcoholics in the relatives of the positive family history subjects varies from study to study.

Moreover, even if disinhibitory behavioral disorders and SA are both associated with low heart rate, low skin conductance orienting responses, and poor conditioning of skin conductance responses to cues of punishment, the direct connection between these patterns of psychophysiological responses and a disinhibited form of SA has not been definitively established. For example, Finn et al. (1994) did not find a relationship between measures of disinhibited personality and skin conductance or heart rate measures in their sons of alcoholics. Additionally, no studies have examined the relationship of autonomic arousal measures with familial risk for both antisocial personality and SA. The extent to which these psychophysiological measures also predict the

onset of an undersocialized form of SA awaits future study.

#### *Reduced amplitude cerebral potentials*

Another line of research, which shows promise for identifying those at risk for disinhibited traits and SA, examines the time-locked electrocortical voltage evoked by task-relevant events. These event-related potentials (ERPs) are recorded in the electroencephalograph (EEG) and averaged over many trials. At roughly 300–600 ms after the presentation of an infrequent or task-relevant stimulus, a relatively large positive wave, referred to as P300 or P3, is frequently observed. Small P3 amplitude has been related to undersocialized behavior, including antisocial personality disorder (Bauer, O'Connor, & Hesselbrock, 1994), impulsivity and aggression in adult prisoners (Barratt, Stanford, Kent, & Felthous, 1997), and antisocial behavior in alcoholics (Branchey, Buydens-Branchey, & Lieber, 1988), and thus represents a candidate marker for early-onset, undersocialized SA (Iacono, 1998).

P3 amplitude has also been associated with familial risk for SA. Elmasian, Neville, Woods, Schuckit, and Bloom (1982) reported that the young adult sons of alcoholics evidenced smaller P3 amplitude compared to the sons of nonalcoholics when receiving a placebo in an alcohol challenge study. Begleiter, Porjesz, Bihari, and Kissin (1984) further found that the younger sons of alcoholics, who themselves had never been exposed to alcohol, manifested smaller P3 than the sons of nonalcoholics. Although not all researchers have replicated the finding of Begleiter et al. (1984), a meta-analysis by Polich, Pollock, and Bloom (1994) indicates that there is a substantial effect of paternal alcoholism on a son's P3 amplitude, one that it is more likely to be seen in studies with younger subjects, visual stimuli, and challenging tasks. Moreover, Pfefferbaum, Ford, White, and Mathalon (1991) found that the P3 amplitude of alcoholics was related to degree of family loading for alcoholism (i.e., number of alcoholic relatives), and not to history of alcohol consumption.

Further support for P3 amplitude being a marker for a disinhibited phenotype broader than alcoholism comes from studies of substance use disorders involving illicit drugs. In adults, reduced P3 voltages relative to control values has been observed in cocaine and heroin addicts both without (Biggins, MacKay, Clark, & Fein, 1997; Branchey, Buydens-Branchey, & Horvath, 1993) as well as with (Biggins et al., 1997) a history of alcoholism. Reduced P3 amplitude have also been associated with long-term cannabis use in adults (but see Patrick et al., 1995, for an alternative explanation; Solowij, Michie, & Fox, 1991), and a paternal history of substance dependence in preadolescent sons (Brigham, Herning, & Moss, 1995). Longitudinal research further indicates that small P3 amplitude in preadolescent children predicts adolescent substance use (Berman, Whipple, Fitch, & Noble, 1993) and abuse (Hill, Steinhauer, Lowers, & Locke, 1995).

Although the functional significance of a P3 amplitude deficit is unclear, it does appear to be related to the presence of a variety of antisocial characteristics and substance abuse, may predict the development of future abuse, and is present in the unaffected relatives of substance abusers. Hill, Steinhauer, and Locke (1995) have suggested that small P3 amplitude seen in offspring of alcoholics reflects a delay in neurophysiological development that is ameliorated by early adulthood. However, Ramachandran, Porjesz, Begleiter, and Litke (1996) reported reduced P3 amplitude in older (mean age: 27.8 years) sons of alcoholics. In any case, more work is needed to confirm the specificity of P3 deficits in undersocialized substance abusers and to relate those deficits to other indicators of disinhibitory psychopathology.

#### *Autonomic and cerebral psychophysiological measures are heritable*

Skin conductance orienting response and conditioning, baseline heart rate and orienting response, and P3 amplitude may all reflect heritable influences on the development of disinhibited behavior. They may reflect risk for a common deficit in inhibitory control, or

they may be related to separate processes contributing independent effects on disinhibited substance abuse. Many of these measures have demonstrated genetic influence. Skin conductance reactivity has been shown to be strongly genetically influenced in a study of MZ and DZ twins reared apart and fits a polygenic-additive model (Lykken, Iacono, Haroian, McGue, & Bouchard, 1988). Resting heart rate, as well, is more similar in MZ twins than DZ twins (Voss et al., 1996), with as much as 77% of the variance in adults being attributable to genetic influences (Russell, Law, Sholinsky, & Fabsitz, 1998). Twin studies also support heritable sources of variance in P3 amplitude (e.g., O'Connor, Morzorati, Christian, & Li, 1994). Recent molecular genetic studies further suggest specific genetic influences on P3. Linkage between P3 amplitude and chromosomes 2 and 6 has been suggested by a large, multisite study (Begleiter et al., 1998). Further, P3 amplitude has been related to the A1 allele at the DRD2 dopamine receptor site (Hill et al., 1998), and a possible association has been found with the CNR1 cannabinoid receptor gene (Johnson et al., 1997). These studies link possible genetic influences on P3 amplitude to neurotransmitter systems implicated in some forms substance abuse and externalizing disorders (Comings et al., 1996).

### **Preliminary Conclusions**

This literature review supports the following tentative elaboration of our hypothesis. There is a heritable, early onset variant of SA characterized by the presence of comorbid psychopathology and behavior associated with antisociality. This SA variant develops in individuals characterized by personality traits associated with behavioral disinhibition (such as low constraint) who are apt to have externalizing childhood disorders such as ADHD, ODD, and CD. These personality traits and childhood disorders are themselves heritable, perhaps reflecting the presence of overlapping genetic factors. Studies of autonomic psychophysiology indicate that hypoactivity has been associated with externalizing disorders of childhood and the development of criminality

and alcoholism. Reduced P3 wave amplitude has shown a relatively robust association to genetic risk for alcoholism especially in young adolescent boys. Diminished P3 may also be associated with antisociality and other forms of SA besides alcoholism. These measures of autonomic and cerebral psychophysiology are themselves heritable. Taken in the aggregate, these findings suggest that heritable, psychophysiological markers may serve to identify those who have inherited a biological vulnerability for the development of the unsocialized variant of SA.

Although these conclusions support our contention that there exists a highly heritable form of SA that reflects a generalized deficit in disinhibitory processes and that can be identified using psychophysiological methods, these findings do not serve to identify the mechanisms underlying the relationship between undersocialized SA and disinhibitory psychopathology and behavior. In order to explicate these mechanisms we have taken a developmental, behavioral genetic approach in the MTFS, a large, longitudinal, multivariate program of research that utilizes a behavioral genetic design. This program of research, described in more detail in the following section, focuses on how a generalized tendency towards behavioral disinhibition is both inherited in SA families and affects the development of SA.

### **Aims of the MTFS**

The MTFS is an ongoing longitudinal investigation of about 1400 preadolescent and adolescent twin pairs and their parents recruited for study approximately 11 or 17 years after the birth of the twins. Families came to our university laboratory for a full-day assessment that included the completion of self-report inventories, clinical diagnostic interviews, and psychophysiological assessment. Twin participants are reassessed in our laboratory every 3 years as they pass through the age of risk for developing substance use psychopathology. The MTFS has several overarching aims that render it well suited to examine the link between behavioral disinhibition and the development of SA.

### *Exploring the nature of genetic influence*

Although evidence from multiple sources points to a genetic influence on the development of substance use disorders, little is known either about the mechanism of genetic influence or the processes by which genetic factors combine with environmental factors to affect the development and course of substance abuse and related phenotypes. Several aspects of the MTFs research design provide an opportunity to address these shortcomings of the existing literature. In attempting to understand how genetic factors might influence SA risk, different strategies are relevant (McGue, 1995). The first involves identifying the specific genes that contribute to SA liability. While molecular geneticists are likely to ultimately achieve this goal, it is unlikely that complex behavioral phenomena like SA will ever be reduced entirely to protein interactions—additional approaches such as those employed by the MTFs are needed. Recognizing that SA is likely to be etiologically heterogeneous and includes a variant characterized by behavioral disinhibition, the MTFs aims to explicate the nature of genetic influence by (a) identifying the major psychological and psychophysiological manifestations of different aspects of SA liability and (b) seeking to determine how these factors both mediate the inheritance of SA risk and are moderated by experiential factors.

### *Use of an inclusive sampling strategy*

The generalizability of much of the twin and family research on alcoholism and substance abuse is limited by the ways in which families have been identified. Ascertainment of families through treatment facilities is likely to result in the overrepresentation of severe cases and the overestimation of the strength of familial influences. Public solicitation of volunteers is almost certain to produce atypical and nonrepresentative samples. Community-based studies that condition the selection of cases on the presence of a particular form of psychopathology ignore the reality that comorbidity (especially externalizing psychopathology) is the rule rather than the exception. More im-

portantly, they ignore the likelihood that there is a yet to be clearly delineated spectrum of phenotypes related to the genetic risk for SA. These problems are circumvented in the MTFs through the adoption of an epidemiological design and by achieving high participation rates (see below) that are likely to minimize the effects of sampling bias.

### *Biosocial perspective*

In searching for the roots of SA-related phenotypes, alcohol and drug researchers have often taken different paths. A strong biological tradition in the alcohol research field has led to the identification of brain differences between alcoholics and nonalcoholics (e.g., Begleiter et al., 1984), biochemical correlates of alcoholism (e.g., Tabakoff & Hoffman, 1991), and the existence of genetic influences on alcoholism risk (McGue, 1995). Alternatively, a strong tradition of psychosocial research in the drug abuse field has led to the identification of the importance of peer influences (Kandel, O'Malley, & Eveland, 1978), attachments to conventional socializing institutions (Petratis, Flay, & Miller, 1995), and perceived drug use norms (Hawkins et al., 1992). Over the past decade, both fields have begun to converge on etiological models of substance use disorders that emphasize the joint contribution of biological and social factors (Leshner, 1997). Combining elements of both approaches, the MTFs aims to identify and characterize genetic and environmental influences on early adolescent substance use, and the subsequent progression to adult substance use and abuse. To this end, the MTFs employs a large number of measures designed to sample broadly variables likely to contribute to our understanding of how SA develops, including measures of externalizing psychopathology, personality, central and autonomic nervous system function, and family environment. Multiple informants are used to collect these data on the twins, including parents, each twin's cotwin, and teachers.

### *Developmental, behavior genetic perspective*

Most behavioral genetic research on SA has been cross-sectional, adopting, at least im-

plicity, a static nondevelopmental perspective—SA occurs because an individual has a relatively large number of risk factors and a relatively small number of protective factors. There are, however, two major limitations to this approach. First, the causal contribution of individual risk factors is, for the most part, indeterminate in a cross-sectional design. Second, because environmental exposure is so poorly assessed retrospectively (Finkel & McGue, 1993), nondevelopmental behavioral genetic designs likely underestimate the importance of specific environmental effects. Most longitudinal investigations of the development of SA, including those based on the study of families, do not employ behavioral genetic designs. Although these investigations can identify associations among variables of interest and provide insight into what factors predict SA-related outcomes, they confound genes and environment, making it difficult to understand the etiology of the observed outcomes.

### **MTFS Research Design**

#### *Participant recruitment*

The intake recruitment process began by identifying the birth records of twins born in the State of Minnesota for birth years extending from 1972 through 1984. A total of 4,386 twin births were identified (53.4% were boys), of which 3,723 pairs (50.8% male) survived infancy intact (perinatal and infant mortality among twins is high). We located the present whereabouts of 3,386 (90.9%) of these twin pairs, with the 3,329 living pairs (50.9% male) constituting our recruitment population. Of these pairs, 1,053 did not meet study entrance criteria (i.e., the twins either lived further than a day's drive from Minneapolis, had a mental or physical handicap that precluded completion of the assessment, or had been adopted by nonrelatives), and 121 pairs were never contacted because we had met annual recruitment goals before their recruitment file had become activated. Of the 2,155 pairs (47.9% male) in our recruitment pool, 372 declined our invitation to participate (giving us a refusal rate of 17.3%) and, 1,383

(48.2% male) completed an intake assessment. Consistent with the demographic profile of Minnesota when the twins were born, the twins are largely Caucasian (97.9%; African American, .3%; Native American, .3%; Hispanic, .2%; Asian, .1%; other or mixed, 1.2%). For these intake families, 99.6% ( $N = 1,376$ ) of the biological mothers and 89.4% ( $N = 1,237$ ) of the biological fathers completed the assessment. Of the 153 nonassessed biological parents, 84 (3% of the total) refused to participate or failed to agree to an assessment date, and 69 were unavailable for assessment due to death or severe illness ( $N = 29$ ), uncertain paternity ( $N = 6$ ), mother asking that father not be contacted ( $N = 13$ ), and unavailability ( $N = 21$ ; out of country, in jail, or unlocatable). In addition, six stepmothers and 95 stepfathers participated, bringing the total number of individuals assessed to 5,471.

An additional 400 families never scheduled and completed an assessment. The existence of this latter group warrants specific comment. Because there were more twin families available in any given year than we could actually assess, it was not possible to schedule all available families. In addition, because the MTFS uses a cohort-sequential design, assessments scheduled for twins born in a given year must be completed in the year scheduled, before the twins become too old to belong to their age cohort. Because of these factors, there were about 400 twin families who were in our recruitment pool and for which some effort was expended to recruit but that we could not have assessed under any circumstances. These unscheduled families were a heterogeneous group that included those for whom the recruitment effort was limited to a single unanswered phone call to families who scheduled but later canceled their appointment.

To investigate potential sampling biases, we obtained a brief self-report survey or telephone interview on 1,607 (82.6%) of the 1,946 nonassessed families in our recruitment pool. There were few large differences between assessed and nonassessed families. Compared to nonassessed mothers and fathers, mean years of education was moderately but significantly higher among assessed

mothers (13.4 vs. 13.7 years) and fathers (13.8 vs. 14.0 years). Although assessed mothers also had significantly, but modestly, higher occupation status than nonassessed mothers, there was no statistically significant difference in the occupational status of participating and nonparticipating fathers. Importantly, assessed and nonassessed families did not differ significantly in (a) self-reported rates of alcoholism or treatment for alcoholism in either mothers (1.6% in assessed vs. 1.9% in nonassessed) or fathers (11.8% vs. 13.5%, respectively), and (b) self-reported rates of depression or treatment for depression in either mothers (12.4% vs. 11.4%) or fathers (6.6% vs. 6.1%). The largest differences between participating and nonparticipating families were for zygosity and cohort, although even here the differences were modest. MZ twins were more common (64.9% vs. 57.9%) and 17-year-olds less common (41.0% vs. 49.1%) among participating as compared to nonparticipating families. These analyses thus indicate that there are minimal differences between participating and nonparticipating families on indicators of socioeconomic status and no differences between the two types of families in self-reported rates of parental psychopathology.

#### *Assessment protocol*

To maximize the longitudinal utility of our observations, our in-person intake and triannual follow-up protocols (supplemented by annual telephone follow-ups) are very similar and include age-appropriate self-report, clinical, and psychophysiological assessments. All interviews and psychophysiological assessments are conducted by staff without knowledge of the subject or the subject's family. Twins who visit our laboratory together are interviewed simultaneously, each in a separate room by a different interviewer. Psychophysiological sessions are also run concurrently. At the end of the clinical interview covering substance use, twins are asked about the substance use behavior of their cotwins. Medical records are obtained in any case where a family member has or develops a significant physical or mental health problem.

*Clinical assessments.* Our assessments cover the major behavioral disorders, including all substance use disorders, conduct and antisocial personality disorder, major depression, and various disorders of childhood. Our interviewers undergo intensive training in which they take a lecture and self-study course on diagnostic interviewing, must pass a written examination covering the DSM disorders we assess, apprentice themselves to seasoned interviewers, and satisfy proficiency criteria. Every interview is tape-recorded and undergoes comprehensive review, and feedback is provided to interviewers on the adequacy of every interview.

Younger adolescents are assessed with the revised version of the Diagnostic Interview for Children and Adolescents (DICA-R; Welner, Reich, Herjanic, Jung, & Amado, 1987). Probes and questions have been added to insure complete coverage of each DSM-III-R and DSM-IV childhood disorder. The mother (or primary caretaker) of the twins is interviewed with the DICA-R—Parent Version (also modified and updated). All the questions asked the child are asked the mother as they pertain to the child. When the twins are older, alcohol, nicotine, and drug use disorders are assessed using the expanded substance abuse module (SAM) developed by Robins, Babor, and Cottler (1987) as a supplement to the World Health Organization's Composite International Diagnostic Interview (CIDI; Robins et al., 1988). We have modified the SAM, again by adding questions to update the instrument. The Structured Clinical Interview for DSM-III-R and DSM-IV is used to assess mood disorder, and an interview developed by project staff provides detailed assessment of the DSM-III, -III-R, and -IV criteria for ASPD. The interviews of the father and mother parallel those for the 17-year-old and older twins.

Diagnostic assignment begins with the review of all the interview data collected at one point in time for each case by pairs of individuals with advanced clinical training. All items scored positive or about which there is any question regarding scoring are reviewed, listening to audio tapes as necessary and using ancillary information from schools, teachers,

and medical records as appropriate. This information is used to code every symptom and diagnostic criterion relevant to the diagnostic systems we use. In addition to coding these symptoms, we also track the source of the information (e.g., child, mother, teacher) used to determine the presence of the symptom. These data are key punched and computer programs based on the algorithms present in the DSM are used to assign diagnoses. We generate diagnoses based separately on information provided by each informant (e.g., the mother or the child) and combine information across informants to yield diagnoses that make the best use of all available information. When combining data from multiple sources to arrive at a best estimate composite diagnosis, evidence that a symptom is present is given more weight than the refusal to acknowledge a symptom, especially when the positive symptom is backed up by a convincing example, indications of impairment, or converging data from the multiple sources. To combine data from the mother and child DICAs, we use as a starting point the provisional rules established by Reich and Earls (1987). Case reviews are always carried out such that the senior clinical staff is unaware of the diagnoses of the other members of the family.

For this report, all of the diagnoses are based on DSM-III-R criteria, the diagnostic system in place when the MTFS was begun, and cover the lifetime of the participants. Diagnoses are considered present if criteria are satisfied at either a "definite" or "probable" level. For a definite diagnosis, all DSM-III-R criteria must be satisfied. For a probable diagnosis, all but one symptom need be present. The probable diagnostic designation allows for case identification in individuals who are not currently symptomatic and who must rely on distant memory to recall what their symptom picture was like when they experienced an acute disorder, a diagnostic strategy that was introduced as part of the Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978). The only diagnosis that was not made at the probable level was that for substance abuse, because this disorder is defined by the presence of a single symptom

in DSM-III-R. In addition to standard DSM diagnostic categories, we also "diagnose" adult antisocial behavior (AAB). This designation derives from the DSM-III-R criteria for antisocial personality disorder, which requires the presence of CD prior to age 15 years and four symptoms of "irresponsible and antisocial behavior since the age of 15." Participants with AAB satisfy the latter requirement by displaying antisocial behavior but do not satisfy criteria for CD. These antisocial individuals are "late bloomers" who are typically ignored in research on antisocial behavior. Although we diagnosed ODD using the DSM-III-R criteria, we deviated from the DSM requirement that ODD not be diagnosed in individuals with CD.

We have examined diagnostic reliability as a function of disorder, informant, subject age, and interview instrument. A total of about 600 subjects, selected to insure adequate representation of the psychopathology we assess, were used for this purpose. All relevant clinical information, including audio tapes, was reviewed by pairs of clinicians who determined the presence or absence of each symptom we assess without knowledge of the original diagnostic assignment. For disorders covered in this article, our best estimate diagnoses yielded the following kappa reliabilities: ADHD (.77), ODD (.71), CD (.81), ASPD (.95), major depression (.82), substance (alcohol, nicotine, cannabis, amphetamines) abuse or dependence (all kappas greater than .91). The reliability of the AAB designation was .95.

*Substance use.* Our interview assessments of substance use and abuse are supplemented by a computer-administered questionnaire self-administered on a touch-screen terminal. The terminal is located in a sound-dampened, private room, thus providing adolescents with an opportunity to report sensitive material related to drug use without having to reveal the information directly to an interviewer. The questionnaire examines quantity, frequency, age of onset, and variability of use related to alcohol, tobacco, and various drugs. Included in the assessment are various probes to identify invalid protocols including the use of fictitious street drugs (e.g., have you ever used bleomy-

cins?) as well as items that should be endorsed by just about everyone (e.g., have you ever seen an adult smoke?).

*Personality.* Personality was assessed by self-report using the 198-item version of the Multidimensional Personality Questionnaire (MPQ), an instrument with excellent psychometric properties (Tellegen & Waller, in press). The MPQ is an omnibus personality inventory consisting of 11 primary scales that load on three higher order factors: positive emotionality (Well-Being, Social Potency, Social Closeness, Achievement), negative emotionality (Stress Reaction, Alienation, Aggression), and constraint (Control, Harm Avoidance, Traditionalism). The 11th primary scale, Absorption, does not load principally on any of the higher order factors.

Individuals high on positive emotionality have a low threshold for experiencing positive emotions and tend to view life as essentially pleasurable. Those high on negative emotionality have a low threshold for experiencing negative emotions, such as fear, anxiety, and anger, and are stress reactive. Constraint captures the complement of behavioral disinhibition. High scorers tend to endorse social norms, act in a cautious and restrained manner, and avoid thrills. Low scorers, by contrast, are risk takers who are unlikely to inhibit behavioral impulses. Prior to their in-person assessment, the older twins and all parents were mailed the MPQ, which they were asked to complete and either return via mail or on their visit.

*Psychophysiology.* To explore the possibility that substance dependence may derive in part from a deficit in an inhibitory control system (e.g., BIS), a subset of MTFs participants was evaluated with a procedure called "cooltest" (Taylor, Carlson, Iacono, Lykken, & McGue, 1999). This task provides an indication of how well individuals can cope with the stress of being exposed to an aversive stimulus, a noxious burst of noise that varied in its predictability. We hypothesized that those with good inhibitory control would be able to take advantage of the predictability of the stimulus, and that the capacity to do so could be indexed by determining if autonomic reactiv-

ity was suppressed when the stimulus was predictable.

The coolest task required participants to watch a sweep second hand move around a clock face in one of two conditions. During predictable trials, the noise was presented when the second hand reached a tick mark on the clock face. In the unpredictable condition, no indication was provided regarding when the noise would be presented. Participants were instructed to "try to stay cool and not react to the loud noise," which consisted of a 2-s blast of 90-dB white noise. The autonomic measures included the skin conductance response to the noise blast and heart rate in anticipation of and following the blast.

Specifically, we hypothesized that individuals with dysfunctional inhibitory control would be unable to take advantage of stimulus predictability to block the aversive impact of the noise blast. Operationally, this would be defined by their showing relatively little difference in their response to the blast whether it is or is not predictable and even larger than normal skin conductance responses to the blast when it is predictable. By contrast, those with good inhibitory control should show smaller responses when the blast is predictable than when it is unpredictable. We also hypothesized that cardiac activity would index the presence of an active coping response (e.g., Ogloff & Wong, 1990). Those with good inhibitory control should show more heightened cardiac rate preceding the predictable blast than preceding the unpredictable blast.

To assess whether the P3 event-related potential (ERP) might tap into the neurophysiological underpinnings of deficits in behavioral inhibitory control, we have included the P3-eliciting cognitive task employed by Begleiter et al. (1984). Participants watch a computer screen while either ovals depicting the superior view of heads or plain ovals appear every few seconds. The heads occur less frequently than the ovals and they require a behavioral response. Both of these features cause the heads to elicit P3 waves. The heads have either a "nose" pointing up or are rotated 180 degrees so the nose points down. An "ear" appears on one side of the head. The subject's task is to press one of two buttons to indicate

on which side of the head the ear appears. Although there are two levels of difficulty to this task (it is harder to perform correctly when the nose points down) and multiple electrode recording sites are used, for simplicity, we have combined the data across difficulty levels and present data for only one electrode site, Pz, the site that has received the most attention in the P3–alcoholism literature. Complete details of our recording procedures can be found elsewhere (Carlson, Katsanis, Iacono, & Mertz, 1999; Katsanis, Iacono, McGue, & Carlson, 1997).

### Findings from the MTFs

In the remainder of this article, we present findings from the MTFs that support and extend our contention that risk for developing SA is genetically influenced and may be mediated by individual differences in an underlying dimension of behavioral disinhibition reflected in undersocialized behavior and characteristic psychophysiological deviations. Because we are in the early stages of this longitudinal study, we have little follow-up data on study participants, none of whom has passed through the age of risk for developing substance use disorders. Because hardly any of the 11-year-old twins have any significant experience with drugs or alcohol, analysis of intake data from this group provides little opportunity to address our hypotheses. Consequently, most of the findings to date reflect analyses of cross-sectional data that are focused on the older twin cohort and the parents of all the twins. Finally, because the MTFs began by studying boys only, the collection and analysis of data from female twins has lagged that of the males, forcing us to focus our early data analytic efforts largely, but not exclusively, on boys.

#### *There is a heritable liability for tobacco, alcohol, and drug use*

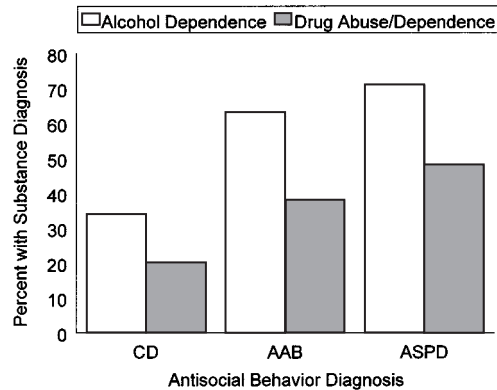
In an analysis based on the first few years of intake of 17-year-olds, we analyzed the heritability of substance use as reported on our computerized substance use questionnaire (Han, McGue, & Iacono, 1999). Five hundred one twin pairs were examined, 179 MZ and

97 DZ pairs of boys and 148 MZ and 77 DZ pairs of girls. Each twin was classified as positive or negative for the lifetime use of alcohol, tobacco, or other drugs used to “get high.” Biometric models were fit separately to the male and female data. These analyses indicated heritabilities for alcohol, tobacco, and other drug use, respectively, of 59, 60, and 33% for the boys and 11, 10, and 11% for the girls. Both models indicated a role for shared environmental factors, with shared environment appearing to be more important for the female twins. Because the gender differences were not statistically significant, a gender invariant model was fit to the combined male and female data. The resulting heritability estimates were 36, 35, and 23%, respectively. The covariation of the three substance use phenotypes was also examined to determine the heritability of a latent phenotypic factor for substance use liability. Genes were deemed to account for 23% of the variance in this factor, shared environment for 63%, and nonshared environment for 14%.

These findings concern substance use and not abuse, an important distinction because genetic and environmental factors associated with the initiation of substance use are not necessarily the same as those leading to sustained use and abuse. Moreover, with the samples available for this preliminary analysis, it is not possible to make precise estimates regarding the differential contribution of genes and shared environment or to reach firm conclusions about possible gender differences. Nevertheless, our findings parallel those of other investigators regarding the relative contribution of genetic and shared environmental factors to substance use (Koopmans, van Doornen, & Boomsma, 1997; Swan, Carmelli, & Cardon, 1996). Candidate environmental factors remain to be identified but could include the influence of neighborhood, school experience, and parental attitudes toward adolescent substance use.

#### *Externalizing psychopathology is associated with SA*

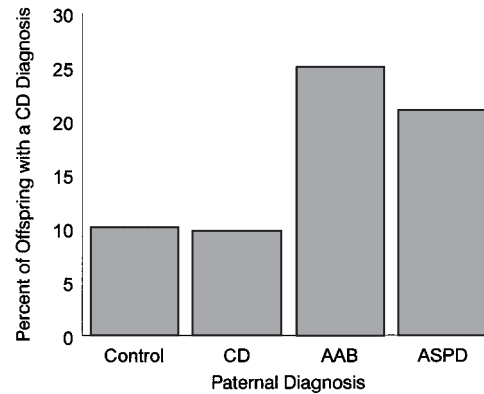
Examination of MTFs fathers demonstrates a strong link between antisociality and heightened risk for SA. Elkins, Iacono, Doyle, and



**Figure 1.** Percentage of fathers with antisocial personality disorder (ASP), adult antisocial behavior (AAB), and conduct disorder (CD) only who have comorbid substance use disorders. Adapted from Elkins et al. (1997).

McGue (1996) showed that risk for SA generally varied as a function of the severity and chronicity of antisocial behavior in these adult men. This investigation was based on data from the first 607 families of male twins that were entered into the study. Fathers from these families were divided into four distinct groups (total  $n = 222$ ). The nonpsychiatric comparison group ( $n = 57$ ) was composed of fathers with no diagnosis or AAB. Those with conduct disorder only ( $n = 62$ ) satisfied DSM-III-R criteria for this disorder but had no more than one AAB symptom. Those with AAB only ( $n = 46$ ) had no more than one CD symptom. The fourth group comprised fathers with ASPD ( $n = 57$ ). These groups were thus roughly ordered according to the severity and persistence of antisocial behavior, ranging from those with little or none to those whose antisocial conduct was limited to adolescence, to those who developed antisocial symptoms as adults, to those whose antisociality persisted from adolescence to adulthood.

Several findings of interest emerged from this study. First, the rates of substance disorder differed significantly across groups (leaving out the nonpsychiatric comparison group that by definition had no diagnoses). As Figure 1 illustrates, fathers with ASPD had rates of alcoholism and illicit drug abuse or dependence that were more than twice those seen in fathers who had CD as adolescents but who



**Figure 2.** Prevalence of conduct disorder (CD) in the offspring of fathers with no antisocial diagnosis and in the children of fathers with antisocial personality disorder (ASP), adult antisocial behavior (AAB), and conduct disorder only. Adapted from Elkins et al. (1997).

did not go on to develop ASPD. Although fathers with AAB only showed rates of disorder that fell between these two groups, their rates were still almost twice those of fathers with CD only. Hence, the AAB group differed little from the ASPD participants while having rates of substance disorder that were much higher than those of the CD group. These findings suggest that risk for SA is especially heightened in those who show antisocial behavior that emerges or persists into adulthood.

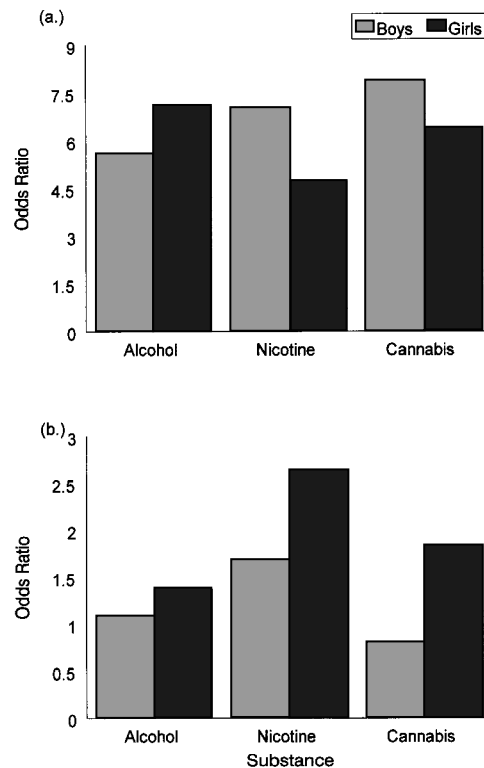
A second interesting finding from this study relates to the antisocial behavior of the 11- and 17-year-old children of these fathers. The rate of conduct disorder differed significantly across the four groups (Figure 2). The children of fathers with ASPD or AAB were about equally likely to have CD, with about 23% of the children manifesting CD. This rate was more than double that of the other two groups, which did not differ and showed a combined prevalence for CD of less than 10%. Taken together, these findings concerning the rate of substance diagnoses in the fathers and the prevalence of CD in their offspring suggest that it is adult antisocial behavior, not juvenile behavior that desists, that is critical to the link between antisociality and SA, a point that we return to below.

Holdcraft, Iacono, and McGue (1998), again focusing on subsets of the fathers of

male twins, investigated how the presence of ASPD heightens the likelihood of other forms of substance use disorder. Two hundred seven alcoholic fathers were divided into groups depending on whether they had comorbid ASPD but not major depression ( $n = 25$ ), comorbid major depression but not ASPD ( $n = 24$ ), and alcoholism with neither major depression nor ASPD (“other” group;  $n = 130$ ) but with at least one other form of psychopathology (CD or other substance use disorder). The dependent variables examined concerned the drug use behavior of the individuals in these groups. By including the major depression and other comorbidity groups in this study, it was possible to determine whether it was comorbidity generally that is associated with drug use among alcoholics or comorbidity that involves antisocial behavior per se.

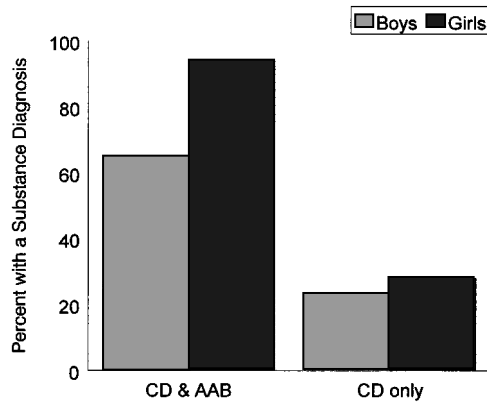
The ASPD alcoholics differed significantly from both the alcoholics with major depression and the other alcoholics on all variables examined. In particular, the ASPD group was found to use more different types of illicit drugs and to use their preferred drug more frequently. ASPD alcoholics were significantly more likely than those in the other two groups to have used cannabis, amphetamines, cocaine, and psychedelics. Interestingly, the ASPD and major depression alcoholics differed little in alcohol use. For instance, these two groups did not differ in age at first alcohol intoxication, years of drinking until intoxicated, and lifetime consumption of alcohol. They also did not differ in the percent treated for alcoholism. These findings suggest that it is the presence of ASPD per se that is associated with heightened SA risk, not merely comorbidity generally or the severity of alcoholism.

Turning to how externalizing psychopathology in the children is related to SA risk, Disney, Elkins, McGue, and Iacono (1999) investigated the association between gender and the spectrum of childhood psychopathology that we hypothesize to be associated with behavioral disinhibition in 578 MZFS 17-year-old boys and 674 girls. Eighty girls and 165 boys had CD without ADHD, 24 girls and 28 boys had ADHD without CD, and 8 girls and 50 boys had both CD and ADHD. These ado-



**Figure 3.** (a) The odds of having a substance use diagnosis when conduct disorder is present while controlling for the effects of comorbid ADHD. (b) The odds of having a substance use diagnosis when ADHD is present while controlling for the effects of comorbid conduct disorder. Adapted from Disney et al. (1999).

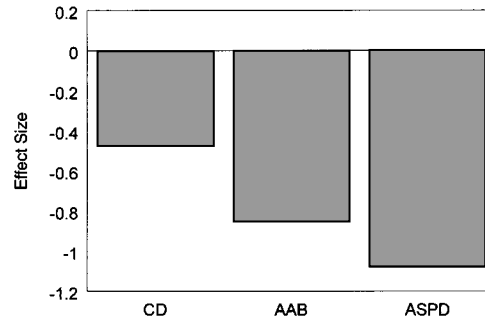
lescents were compared to 562 girls and 335 boys with neither disorder. Boys and girls with CD were significantly more likely to be currently using tobacco or alcohol, and if they used either of these substances they used them more frequently than comparison subjects. They were also more likely to have nicotine dependence and alcohol or illicit drug abuse of dependence. Figure 3a indicates the odds of having a comorbid SA diagnosis as a function of having a diagnosis of CD while controlling for the effects of ADHD. For both genders, the odds of having a substance diagnosis are substantially elevated. Although ADHD was similarly associated with increased risk for SA, when the effect of CD was controlled, with one exception, the diagnosis of ADHD had little effect on substance



**Figure 4.** Percentage of 17-year-old boys and girls with substance use disorders as a function of whether they have conduct disorder (CD) that is (CD & AAB) or is not (CD only) followed by the development of adult antisocial behavior (AAB). Adapted from Disney et al. (1999).

use and abuse outcomes in either gender (Figure 3b). The one exception, for nicotine dependence, indicated that 17-year-olds with lifetime ADHD diagnoses were at increased risk for this addiction (a finding consistent with Milberger, Biederman, Faraone, Wilens, & Chu, 1997). Although these data could be interpreted as providing weak evidence that ADHD is a risk factor for SA other than nicotine dependence, ADHD, which by definition onsets prior to age 7 years, is itself associated with heightened risk for CD (Wilens & Biederman, 1993). In fact, in our sample, over half of all cases of ADHD had comorbid CD.

The presence of AAB symptoms developing between the ages of 15 and 17 years in these teenagers was also related to SA risk. Disney et al. (1999) subdivided adolescents with CD into two groups, those with at least two AAB symptoms (88 boys, 33 girls) and those with CD only (127 boys, 55 girls). Compared to boys and girls with CD only, boys and girls with both CD and AAB were about 3 times more likely to have a substance abuse or dependence diagnosis (Figure 4). These findings suggest that it is the persistence of antisociality past age 15 years that is associated with heightened risk for SA. Furthermore, they complement the findings from MTFS fathers reviewed above indicating that



**Figure 5.** Effect sizes indicating the degree to which MPQ constraint scores are lower than those of normal fathers for MTFS fathers with conduct disorder (CD), adult antisocial behavior (AAB), and antisocial personality disorder (ASPD). Adapted from Elkins et al. (1997).

adult antisocial behavior, rather than adolescent limited behavior, is strongly associated with the development of SA.

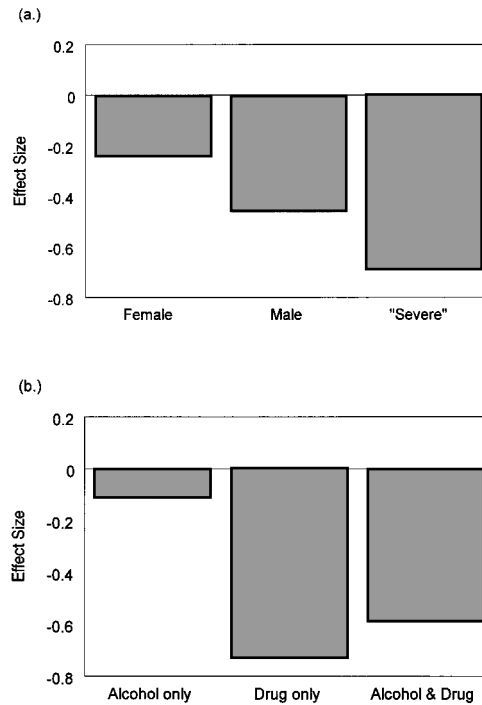
#### *Low constraint is associated with externalizing psychopathology and SA*

Several MTFS publications have explored the link between personality, externalizing disorders, and SA to evaluate the hypothesis that low constraint is associated with externalizing psychopathology and SA. Elkins et al. (1996) examined the link between constraint and externalizing psychopathology in MTFS fathers who took the MPQ. Consistent with the other findings from this study reviewed in the preceding section indicating that ASPD and AAB identify similar individuals, the ASPD and AAB fathers did not differ in constraint. In planned contrasts, both of these groups combined scored significantly lower than the CD and control groups. In turn, the CD group scored significantly lower on constraint than the control group. These results are summarized in Figure 5, which depicts how much lower the three externalizing groups scored on constraint compared to normal fathers in units that reflect the size of the effect. As the figure indicates, a substantial effect size exceeding .8 characterizes the AAB and ASPD groups. In the study of alcohol comorbidity by Holdcraft et al. (1998), the alcoholic fathers with comorbid ASPD had significantly lower MPQ

constraint scores than the nonalcoholic control participants. Collectively, these findings indicate that low constraint is associated with antisocial forms of psychopathology and that scores of this MPQ super factor are negatively related to the severity and chronicity of antisociality.

McGue, Slutske, and Iacono (in press) and McGue, Slutske, Taylor, and Iacono (1997) explored the relationship between personality and SA in MTFs parents. In the first of these publications, the link to alcoholism was examined (McGue et al., 1997). Parents were designated as alcohol dependent (303 fathers and 103 mothers) or nonalcoholic (304 fathers and 770 mothers). Those in the latter group, in addition to not being alcoholic, also did not satisfy criteria for illicit drug abuse or dependence or ASPD. The results, summarized according to effect size in Figure 6a, indicated that both men and women alcoholics had depressed constraint scores. There was no significant interaction between group membership and gender. A cluster analysis was carried out to identify alcoholic subtypes. This analysis yielded two interpretable clusters, but only for the men, identified as "moderate" ( $n = 250$  men) and "severe" ( $n = 54$  men) alcoholism. Compared to the moderate group, the severe group had more CD, ASPD, illicit drug abuse and dependence, relatives with problem drinking, and an earlier age of alcoholism onset. They were thus similar to the early onset, high family loading, antisocial alcoholics who have been identified in the other typological models of alcoholism referred to previously (Babor et al., 1992; Cloninger, 1987; Morey & Blashfield, 1981). As expected, the severe alcoholics had especially low constraint scores compared to control parents (Figure 6a).

In the second of these studies, McGue et al. (in press) examined how the structure of personality might be differentially related to alcoholism and illicit substance abuse or dependence. MTFs parents (1,384 mothers and 1,314 fathers) composed four groups as follows: those with neither an alcohol nor drug disorder ( $n = 1,696$ ), those with alcoholism but no drug disorder ( $n = 363$ ), those without alcoholism but with a drug disorder ( $n = 175$ ),



**Figure 6.** Effect sizes indicating the degree to which MPQ constraint scores were lower than those of normal parents in parents with substance use disorders. (a) Data are presented for male and female alcoholics without regard to the possible presence of any comorbid psychopathology. A subgroup of male alcoholics, identified as "severe," reflects the presence of externalizing psychopathology, illicit drug use disorders, early onset, and a positive family history for excessive drinking. (b) Male and female parents were combined to form three groups: alcoholics without an illicit drug use disorder diagnosis (alcohol only), those with an illicit drug disorder without comorbid alcoholism (drug only), or who had both alcoholism and an illicit drug use disorder. Adapted from McGue et al. (1997, in press).

and those with both alcoholism and a drug use disorder ( $n = 173$ ). For both men and women, CD was elevated in the three affected groups. The diagnosis of ASPD significantly differentiated the four groups, especially for men, where those with both alcoholism and illicit drug abuse or dependence were more than 3 times as likely to possess this diagnosis (prevalence of ASPD in this group: 23.3%) as those in any of the other three groups. With respect to the MPQ analyses, interesting differences emerged between alcohol and drug

diagnoses (Figure 6b). Alcoholism in the absence of a comorbid drug use disorder was not associated with low constraint. Parents with a drug use disorder, including those with comorbid alcoholism, were low in constraint. No significant interactions with gender were observed. Overall, the results suggest that the association observed in the MTFS as well as other studies between low constraint and alcoholism may be attributable to a subset of alcoholics who also abuse illicit drugs. Failures to observe similar effects in prior alcoholism research are likely due to the lack of consideration of comorbid drug use disorders.

Taken collectively, these findings from the MTFS clearly support and extend existing literature by fleshing out the association among SA disorders, externalizing psychopathology, and personality. They are broadly consistent with the work of other investigators on the typology of alcoholism. They also suggest the existence of a developmental pathway to SA characterized by unsocialized behavior and psychopathology. Factors that influence progress along this pathway remain to be determined, but our data are consistent with a model that begins with a heritable predisposition to be low in constraint. Children especially low on this personality dimension are apt to be impulsive and develop childhood externalizing disorders, like ADHD or ODD leading to CD, or CD and delinquent behavior. The combination of predisposition, expressed psychopathology, and unsocialized behavior serve to heighten the risk for SA. Whether the likelihood of all forms of SA are increased is not clear, but our data suggest considerable overlap for nicotine, alcohol, and illicit drug dependence outcomes. Also undetermined is the role substance exposure and use plays in the development of SA, from initiation to regular use, to abuse, and ultimately to dependence.

*Heritable individual differences in autonomic reactivity are associated with SA*

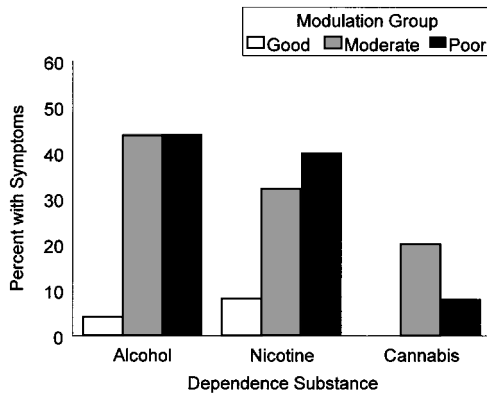
In part to elucidate the psychophysiological substrate underlying individual differences in behavioral disinhibition, a subset of MTFS participants was evaluated with our “coolest”

procedure. This paradigm was intended to determine if participants could inhibit their autonomic reactivity while anticipating a noxious burst of noise that varied in its predictability.

To investigate this possibility, we selected from 150 seventeen-year-old males who successfully completed this procedure 50 individuals who represented the extremes of electrodermal modulation in response to the two types of stimuli. First, we calculated a modulation score for each participant. This score was defined as the skin conductance response to the unpredictable blast stimuli minus the response to the predictable blasts divided by the response to the unpredictable blasts. This score thus reflected the proportionate change in skin conductance amplitude when the blast was made predictable. Good modulators ( $n = 25$ ) generated positive modulation scores, indicating they responded more to the unpredictable blasts. Poor modulators ( $n = 25$ ), generating negative scores, showed the reverse pattern. Moderate modulators ( $n = 25$ ) were selected from the middle of the modulation score distribution and had positive scores that were intermediate to those of these other two groups.

Scores on the modulation index appear to be heritable. The 150 coolest participants included 41 pairs of MZ and 23 pairs of DZ twins. Although these sample sizes are not large enough to justify fitting biometric models to the data, the intraclass correlation indexing twin similarity was significant for the MZ twins,  $r_{MZ} = .42$ . The DZ twin correlation of .29, although obviously less than the MZ correlation, did not differ significantly either from zero or the MZ value, a finding that was not surprising given the limited power to detect significance from such a small sample. The estimated heritability from these data was .26 (Falconer method).

The major dependent variable of interest was the number of DSM-III-R symptoms of substance use disorder. Consistent with expectation (see Figure 7), the two extreme groups differed significantly in their counts of symptoms of alcohol, cannabis, and nicotine dependence, with the good modulators showing little evidence of dependence on any of these substances. The symptom dependence

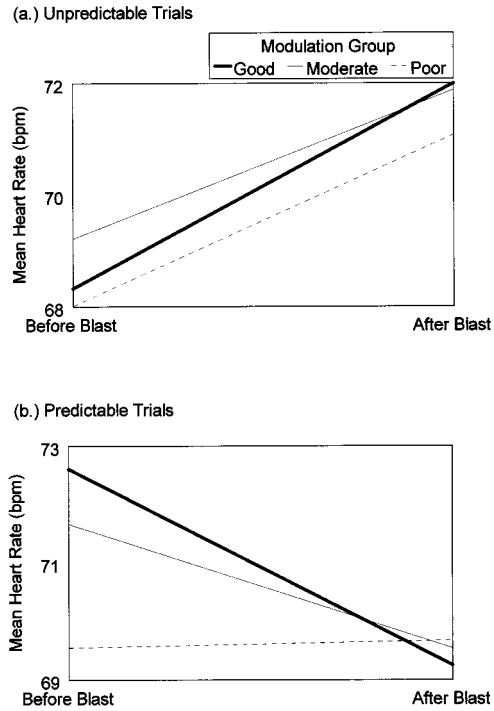


**Figure 7.** Percentage of 17-year-old males with symptoms of different types of substance dependence as a function of their ability to modulate their electrodermal reactivity to predictable aversive stimuli during the coolest procedure. Good modulators were individuals who gave much smaller electrodermal responses to temporally predictable than unpredictable stimuli while poor modulators showed the opposite response pattern. Moderate modulators fell between these two extremes. Adapted from Taylor et al. (1999).

counts of the moderate modulators fell between those of the other two groups. The cardiac activity of the good and poor modulators also differed. Unlike good modulators, poor modulators failed to show cardiac acceleration prior to the blast on the predictable trials (Figure 8). These findings thus suggest that a deficit in inhibitory control related to the capacity to modulate the psychological impact of a predictable aversive stimulus is associated with SA.

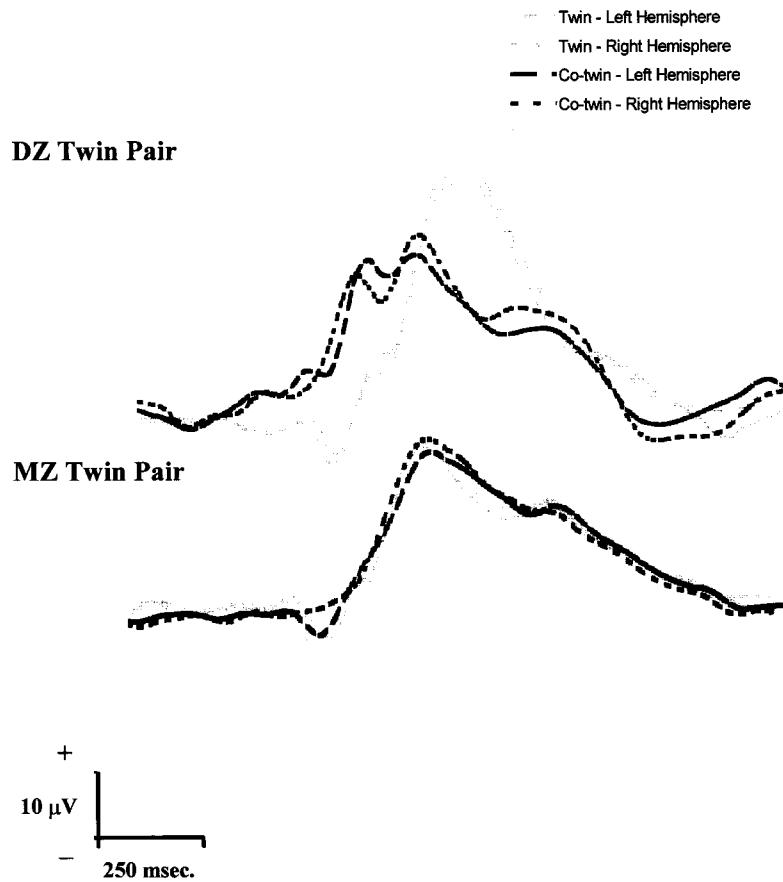
*Heritable individual differences in P3 amplitude are associated with SA*

To determine the heritability of P3 amplitude in the rotating heads task, we compared the degree to which P3 amplitude was similar for members of our MZ and DZ twin pairs (Katsanis et al., 1997). Only 17-year-old boys were available for this analysis. The results indicated that about 79% of the variance in P3 amplitude was genetically determined. As Figure 9 illustrates for individual twin pairs, the P3 amplitudes of the MZ boys were quite similar. To prepare this figure, the average ERP depicting P3 amplitude recorded from



**Figure 8.** Heart rate change during coolest before and after a noxious blast of noise on trials where the stimulus was temporally (a) unpredictable or (b) predictable. See Figure 7 caption for a characterization of participants with good, moderate, and poor electrodermal modulation. Adapted from Taylor et al. (1999).

the left hemisphere (at electrode site P3) was plotted along with that from the right hemisphere (at P4) for each member of each twin pair. For the DZ pair, there is obvious within-twin similarity across hemispheres: the ERP recorded from the left and right hemisphere within an individual is quite similar. However, each DZ twin's ERP is distinctly different from his cotwin's ERP. For the MZ pair, the four plots are superimposed upon one another, indicating high similarity. This figure suggests that for members of a MZ pair, the within individual similarity across hemispheres is equal to the similarity across members of a twin pair. To formally assess this possibility, P3 amplitude recorded from the right hemisphere was correlated with that from the left hemisphere both within individuals and across members of a twin pair for both MZ and DZ twins. The correlation was

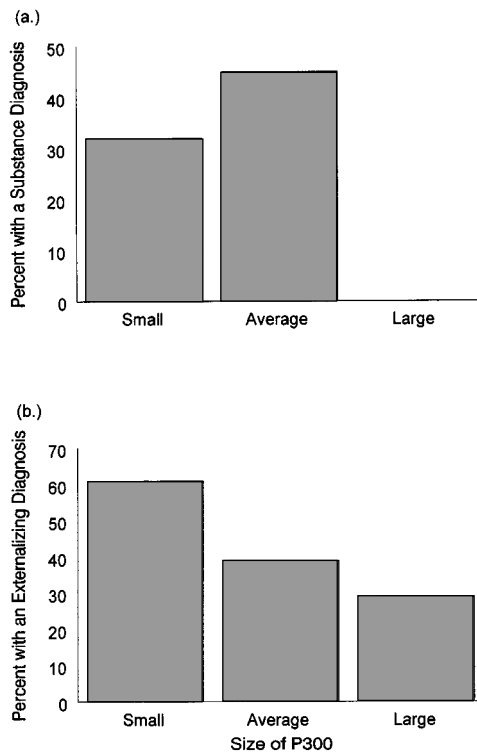


**Figure 9.** Averaged event-related potentials from two MZ and two DZ twins recorded from electrodes placed over the left and right hemispheres of their brains, illustrating that identical twins are as similar to each other as they are similar across hemispheres in their own brains.

.87 within individuals. For MZ participants, the correlation between P3 amplitude from one hemisphere in one twin with P3 amplitude from the other hemisphere in his cotwin was .82. The corresponding cross-twin correlation in DZ twins was .28. This correlational analysis indicates that MZ twins are about as similar to themselves in P3 amplitude across hemispheres as they are to their cotwins.

In a subsequent investigation based on all of the 17-year-old male P3 data, we addressed the hypothesis positing that small P3 amplitude is likely to be associated with externalizing psychopathology and SA (Carlson et al., 1999). Participants were selected from the extremes of the distribution of P3 amplitudes such that two groups were formed, one at psychophysiological high risk for SA because

members had very small P3s and the other at low risk because P3 was quite large. An “average” amplitude group was formed from the middle of the P3 distribution, providing a total sample of 93 boys evenly split across the three groups. Several significant differences emerged among groups (Figure 10a). None of the individuals in the large P3 group had a substance use diagnosis. The psychophysiological high-risk group, those with small P3 amplitudes, contained significantly more cases of alcohol, illicit drug, and nicotine dependence than the large P3 group. Similar results were found for externalizing disorders, which in this case included the childhood disorders of ADHD, CD, and ODD and AAB (Figure 10b). The rate of disorder was highest in the small P3 group, which differed signifi-



**Figure 10.** Percentage of 17-year-old boys with (a) a substance use diagnosis or (b) a diagnosis of externalizing disorder as a function of the size of their P3 waves. Individuals with large or small P3 waves were selected from the extremes of the distribution of P3 size for 17-year-olds. Those with average amplitude P3 were selected from the middle of the distribution. Adapted from Carlson et al. (1999).

cantly from the large amplitude group. These findings indicate that those selected for the presence of the hypothetical endophenotype identifying genetic risk for SA had substantially more manifest psychopathology related to behavioral disinhibition and SA than those without it.

#### *A cumulative risk index for behavioral disinhibition*

Collectively these MTFs findings are consistent with several important conclusions. There is a strong association between indicators of behavioral disinhibition and SA. Fathers with ASPD or AAB are especially likely to have problems with both alcohol and illicit drugs.

Adolescent youth with externalizing psychopathology, especially CD that evolves into AAB, have high rates of SA. The personality dimension of low constraint is associated with CD, AAB, and ASPD. It is also associated with an undersocialized type of alcoholism that is comorbid with illicit drug abuse, as well as illicit drug use disorders in the absence of comorbid alcoholism.

These findings, coupled with those of other investigators reviewed in the introduction to this paper, suggest there are a number of risk indicators pointing to heightened vulnerability for SA in adolescents. Some of this risk follows from the status of their parents, particularly their fathers, and is elevated if a father has alcoholism together with an illicit drug use disorder, AAB, or ASPD. A history of childhood externalizing disorder or antisocial behavior increases the likelihood that a youth will develop SA, as does the presence of low constraint.

In this section, we examine the interaction of these parental and offspring risk factors and their association with SA outcomes, as characterized by the presence of alcoholism, nicotine dependence, or illicit drug abuse or dependence, assessed at intake in our cohort of 17-year-old boys. Specifically, preliminary analyses that follow examine the degree to which (a) SA outcomes are associated with a paternal history of alcoholism, and especially “undersocialized” paternal alcoholism; (b) the relationship between paternal alcoholism and SA outcomes is mediated by a history of offspring undersocialized behavior; (c) the relationship between undersocialized behavior and SA outcomes owes in large part to common genetic influences; and (d) reduced P3 amplitude serves as a marker of risk conferred by paternal status and the presence of offspring undersocialized behavior.

Asked if they have ever used specific substances, many of our 578 seventeen-year-old boys indicated that they had tried alcohol (74.2%), nicotine (69.2%), and drugs (20.6%), even though these substances are illegal at their age. About a sixth of the sample constitute early-onset cases dependent on alcohol or tobacco (see Table 1), and about 6% were drug dependent, with cannabis (5.4%) and

**Table 1.** Percentage of 17-year-old boys of boys with substance dependence diagnoses and undersocialized risk indicators as a function of paternal alcoholism diagnosis

Condition of Sons	Percent Affected ( <i>N</i> = 489–578)	Alcoholism Status of Father			<i>N</i>	$\chi^2(2)$	<i>p</i> Value
		Nonalcoholic ( <i>N</i> = 270–302)	“Socialized” Alcoholic ( <i>N</i> = 116–132)	“Undersocialized” Alcoholic ( <i>N</i> = 60–86)			
<b>Substance use diagnosis</b>							
Nicotine dependence	15.4	10.6 <sup>a,b</sup>	17.4 <sup>a</sup>	25.6 <sup>b</sup>	520	12.88	.002
Alcohol dependence	14.7	9.3 <sup>a,b</sup>	15.9 <sup>a</sup>	22.1 <sup>b</sup>	520	10.93	.004
Illicit drug dependence	6.1	4.0 <sup>b</sup>	4.5 <sup>a</sup>	11.6 <sup>a,b</sup>	520	7.94	.019
<b>Undersocialized risk indicators</b>							
ADHD	9.2	5.0 <sup>a,c</sup>	10.6 <sup>a,b</sup>	19.8 <sup>b,c</sup>	520	18.86	<.001
Conduct disorder	37.2	30.5 <sup>b</sup>	34.1 <sup>a</sup>	53.5 <sup>a,b</sup>	520	15.65	<.001
ODD	18.7	12.6 <sup>a,b</sup>	20.5 <sup>a</sup>	26.7 <sup>b</sup>	520	11.12	.003
AAB	9.9	7.6 <sup>a</sup>	9.8	15.1 <sup>a</sup>	520	4.45	.108
Police contact	23.5	19.5	24.0	28.0	509	3.18	.204
Low constraint	13.3	13.7	8.6 <sup>a</sup>	20.0 <sup>a</sup>	446	4.60	.100

Note: ADHD, attention-deficit–hyperactivity disorder; AAB, adult antisocial behavior past age 15 years; ODD, oppositional defiant disorder. Entries in the same row with the same superscript differ significantly from one another,  $p < .05$ .

amphetamine (1.4%) constituting the drugs on which dependence was most common.

#### *Familial transmission of early-onset SA*

To investigate the familial transmission of SA risk and assess the impact of alcoholism heterogeneity on familial transmission, we classified our sample of 17-year-old males according to history of paternal alcoholism. Three offspring groups were formed according to whether their biological fathers (a) had a history of other antisocial behavior (i.e., AAB, ASPD, or illicit drug abuse or dependence; designated “undersocialized alcoholics” in the table), (b) did not have a history of other antisocial behavior (designated “socialized alcoholics”), or (c) were nonalcoholic. The remaining offspring could not be classified because we did not have diagnostic information on their biological fathers ( $N = 58$ ). Table 1 reports the rates of SA diagnoses in these three offspring groups. A paternal history of alcoholism was significantly predictive of all three SA outcomes. The rate of SA diagnosis was more than twice as high among sons of undersocialized alcoholics compared to sons of nonalcoholics, while sons of socialized alcoholics were at intermediate risk.

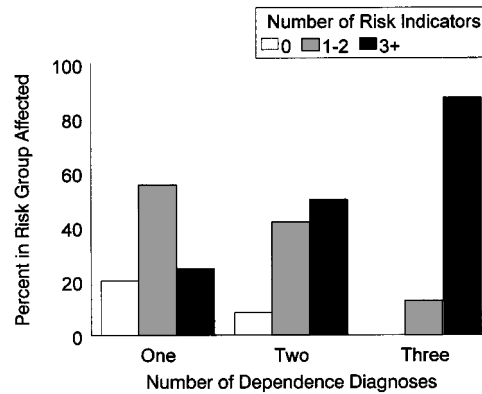
To further explore the relationships among

paternal alcoholism, behavioral disinhibition, and SA outcomes, we rationally developed an offspring “risk index” based on the presence of externalizing psychopathology and low constraint. The six indicators used to define this index, along with their prevalence in our 17-year-old male sample, are listed in the bottom of Table 1. The first four items in the index are DSM-III-R diagnoses. Given the findings of others indicating that criminal acting out is a powerful predictor of subsequent maladjustment and SA (e.g., West & Farrington, 1977), we included an additional, “non-DSM”-based source of information about undersocialized behavior extracted from interviews with the youth and his mother. The item “trouble with the police” was scored positive if the boy ever had police contact for problems other than traffic offenses. Low constraint was considered present if the MPQ Constraint score fell one standard deviation below the mean for 17-year-old boys. Each indicator was present in 9% or more of the boys, with a diagnosis of (probable or definite) CD being the most prevalent single factor in the index. Forty-five percent ( $N = 260$ ) of the boys did not have even one risk indicator, 40% ( $N = 232$ ) had one or two risk indicators, and 15% ( $N = 86$ ) had three or more. The risk index shows good internal consistency re-

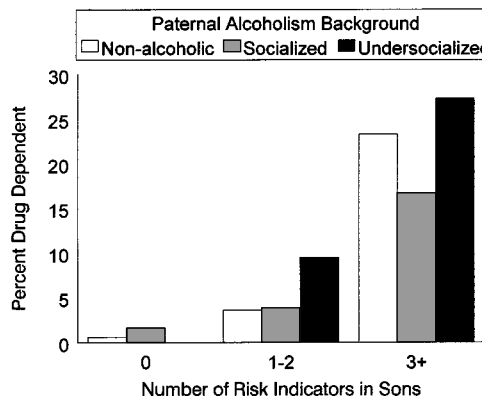
liability (Cronbach's alpha: .60); the correlations between each item and the total scale score (obtained by summing the number of individual items present for a person) with that item removed ranged from .27-.43 (median: .32).

The lower half of Table 1 also summarizes the relationship between each of the six indicators and paternal alcoholism. All of the risk indicators were more common in the children of the undersocialized alcoholics, with those in this group being about twice as likely to have the indicator as the offspring of nonalcoholic fathers. For all but one indicator (Constraint), the offspring of socialized alcoholics showed values intermediate to those of the other two groups. The biserial correlations between the risk index (number of risk indicators present) and SA were large and statistically significant for alcohol ( $r = .60, p < .001$ ), nicotine ( $r = .66, p < .001$ ), and illicit drug ( $r = .60, p < .001$ ) dependence. In fact, the rates of nicotine, alcohol, and drug dependence were all at least 10 times greater in those having three or more of the risk indicators than in those having none of the risk indicators. In addition, the risk index score predicted multiple substance dependence diagnoses. As Figure 11 indicates, all participants with three concurrent substance dependence diagnoses had at least one risk indicator, with about 90% having a risk index score of three or more. Over 90% of those with two dependence diagnoses had at least one risk indicator. These findings indicate a strong association between the presence of one or more indices of behavioral disinhibition and substance dependence.

Given its significant association with both paternal alcoholism and SA risk, it is important to determine whether the risk index mediates the familial transmission of SA risk. For each SA diagnosis, we tested for mediation using a two-factor logit analysis, where paternal alcoholism (three levels) and risk index (three levels) were the two independent variables, and SA diagnosis (two levels) was the dependent variable. For all three SA diagnoses, the results of the logit analysis were the same. The interaction effect was not statistically significant ( $p > .15$  in all cases), but the risk index was significantly predictive of SA



**Figure 11.** Percentage of 17-year-old boys with 0, 1-2, or 3 or more risk indicators as a function of how many concurrent substance dependence diagnoses a person has, indicating that the more diagnoses present, the greater the likelihood an individual will have three or more risk indicators.



**Figure 12.** Percentage of offspring with drug dependence as a function of paternal alcoholism and socialization and the number of risk indicators present in the offspring, indicating that it is the number of risk indicators present in the offspring, not paternal status, that is associated with elevated risk for drug dependence.

diagnosis after controlling for the effect of paternal alcoholism,  $\chi^2(2) > 34.7, p < .001$ , in all cases. Conversely, the effect of paternal alcoholism was not significantly associated with SA outcome once the effect of the risk index had been controlled ( $p > .15$  in all cases).

Figure 12 illustrates the results of the logit analysis for one of the SA diagnoses. As is evident, regardless of paternal alcoholism background, the rate of illicit drug depen-

dence increases substantially as a function of the risk index. Illicit drug dependence is not, however, associated with paternal alcoholism once the relationship of the latter to the risk index has been taken into account. These results suggest that the effect of paternal alcoholism on early-onset SA is mediated entirely by its effect on the risk index. That is, the familial transmission of early-onset SA may owe to the transmission of a general disposition towards behavioral disinhibition, rather than to the transmission of SA per se.

*Nature of the relationship between undersocialized behavior and SA*

These results establish the importance of the risk index in both the prediction and familial transmission of SA risk. Our twin-family design allows us to further characterize the nature of the risk index by determining the extent to which variation on the risk index is associated with genetic and environmental factors. The polychoric correlation between the risk index scores of two MZ twins in our sample was .67 ( $N = 188$  pairs, 95% confidence interval of .54–.78). The comparable correlation in our sample of 101 DZ twins pairs was .26 (95% confidence interval of .02–.47). The MZ twin correlation is both substantially and significantly larger than the DZ twin correlation,  $\chi^2(1) = 11.13$ ,  $p < .001$ , suggesting that genetic factors contribute substantially to variation on the index.

In order to estimate the contribution of genetic ( $a^2$ ), shared environmental ( $c^2$ ), and non-shared environmental ( $e^2$ ) factors to variability in the risk index, the twin data were analyzed using standard biometrical methods. Briefly, under the assumption that all genetic effects are additive, there is no assortative mating, and the environmental contribution to twin similarity is the same for MZ and DZ twins (i.e., the so-called Equal Environmental Similarity Assumption), the expected MZ and DZ twin correlations are given by

$$r_{\text{MZ}} = a^2 + c^2; \quad r_{\text{DZ}} = \frac{1}{2}a^2 + c^2.$$

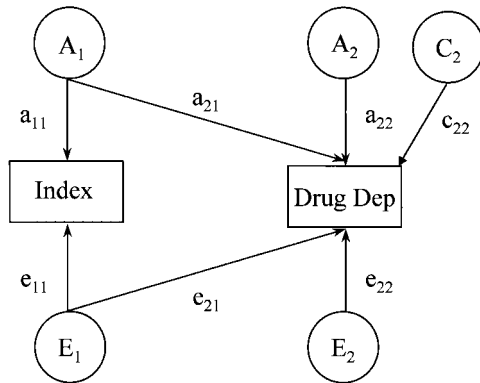
Estimates of the three variance components and the fit of this model to the observed twin

data were determined using the Mx software package (Neale, 1997). The three-parameter model fit the twin data well,  $\chi^2(12) = 14.6$ ,  $p = .26$ . Variance component estimates (95% confidence intervals) were .671 (.299, .769) for  $a^2$ , .000 (.000, .326) for  $c^2$ , and .329 (.231, .454) for  $e^2$ . These analyses thus indicate that the risk index is substantially heritable, with the relevant environmental factors being those that are not shared by reared-together relatives.

Given its substantial heritability, it becomes relevant to determine the extent to which the risk index can account for heritable effects on early onset SA. This issue can be addressed using multivariate genetic analyses, which we will illustrate for illicit drug dependence. In order to increase the sensitivity of these multivariate analyses, twins were considered to have a drug dependence diagnosis if they met DSM-III-R criteria for drug dependence at either their intake or first 3-year follow-up assessment. In our sample of 17-year-old boys, the probandwise concordance (cf. McGue, 1992) for illicit drug dependence was 54.5% in MZ twins and 38.9% in DZ twins, implying heritable effects on illicit drug dependence. To determine the extent to which these heritable effects could be attributed to heritable effects on the risk index, we fit the bivariate model depicted in Figure 13.

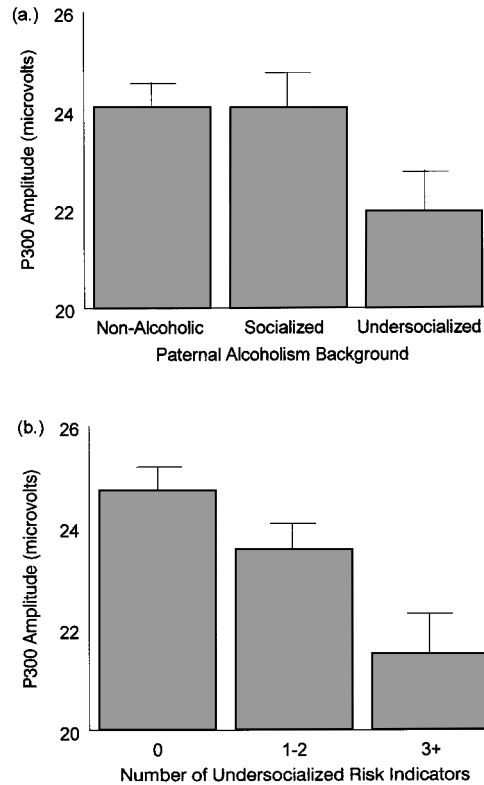
The relationship between illicit drug dependence and the risk index is modeled using a standard two-factor Cholesky decomposition (Loehlin, 1998), under the assumption that illicit drug dependence can be represented as a threshold character (cf. Falconer, 1965). That is, additive genetic effects on illicit drug dependence are decomposed into those attributable ( $A_1$ ) and those not attributable ( $A_2$ ) to additive genetic effects on the index. A similar decomposition is made for nonshared environmental influences ( $E_1$  and  $E_2$ ). Because we found no evidence for shared environmental effects on the risk index (there is no  $C_1$  because this value was zero), however, shared environmental effects on illicit drug dependence are not decomposed.

When this bivariate model was fit to the twin data, estimates of the percentage of variance in the liability to develop illicit drug de-



**Figure 13.** Bivariate Cholesky Model for Drug Dependence and the Socialization Index. In the bivariate model, additive genetic (A) and nonshared environmental (E) effects on drug dependence are decomposed into a portion attributable to additive and nonshared environmental effects on the index (denoted by the “21”-subscripted paths), and a residual portion (denoted by the “22”-subscripted paths). Because our univariate analyses indicated shared environmental effects (C) on drug dependence but not the index, only a residual path is shown for this factor.

pendence associated with additive genetic, shared environmental, and nonshared environmental factors were 52.4%, 22.4%, and 25.2%, respectively. Thus, like the risk index, illicit drug dependence appears to be substantially heritable, but, unlike the index, we found evidence for shared environmental influences on illicit drug dependence. When the additive genetic and nonshared environmental effects on illicit drug dependence were partitioned into effects attributable and not attributable to the risk index an interesting pattern emerged. The total heritability of .524 for illicit drug dependence was partitioned as .445 being attributable to heritable effects on the risk index (as represented by the effect of  $A_1$  via pathway  $a_{21}$  in Figure 14) and .079 being residual (the effect of  $A_2$  via pathway  $a_{22}$ ); the former estimate is statistically significant while the latter is not. The total nonshared environmental component of .252 was partitioned as .004 being attributable to nonshared influences on the risk index (the effect of  $E_1$  on drug dependence via path  $e_{21}$ ) and .248 as residual (the effect of  $E_2$  via path  $e_{22}$ ); the latter estimate is statistically significant while



**Figure 14.** Mean P3 amplitude (with standard error) in (a) offspring as a function of paternal alcoholism and socialization status, and (b) 17-year-old boys as a function of the number of undersocialized risk indicators.

the former is not. Because there is no evidence for shared environmental effects on the index, the entire shared environmental influence on illicit drug use (.224) was associated with residual effects (the effect of  $C_2$  via path  $c_{22}$ ). These analyses thus show that the association between illicit drug dependence and the risk index was mediated almost entirely by common genetic effects (there was almost no unique genetic effect,  $A_2$ , on drug dependence) and that heritable influences on early-onset illicit drug dependence is due almost entirely to heritable influences on the risk index. Only unshared environmental effects (an example of which might be association with delinquent peers) were evident for the risk index, but both shared (e.g., sharing a household where drugs were available) and unshared influences (e.g., having peers who use

drugs) were evident for the development of illicit drug dependence.

### *P3 as a marker of SA risk*

We hypothesized that reduced P3 amplitude would be indicative of familial risk for the undersocialized type of alcoholism. Specifically, we tested the following a priori hypotheses by way of pooled variance planned contrasts: (a) the sons of undersocialized alcoholics have smaller P3 amplitude than the sons of nonalcoholics, (b) the sons of undersocialized alcoholics have smaller P3 than the sons of socialized alcoholics, and (c) the sons of socialized alcoholics have smaller amplitudes than the sons of nonalcoholics. We elected to use directional tests because of the specific nature of our hypotheses, and the support provided by past findings suggesting that P3 amplitude appears to be small in the sons of alcoholics (Polich et al., 1994) and other substance abusers (Brigham et al., 1995), and that this may be especially true of the sons of aggressive or antisocial alcoholics (Begleiter, Porjesz, Rawlings, & Eckardt, 1987; Branchez et al., 1988). The means and standard errors for the sons of undersocialized alcoholic men, socialized alcoholic men, and nonalcoholic men are depicted in Figure 14a. The planned contrasts revealed that, as predicted, the sons of undersocialized alcoholics had reduced P3 amplitude compared to the sons of nonalcoholics,  $t(417) = 2.03$ ,  $p < .05$ . Also, as predicted, this effect does not appear to be driven by familial alcoholism alone as the sons of undersocialized alcoholics had smaller P3 amplitude than the sons of socialized alcoholics,  $t(417) = 1.78$ ,  $p < .05$ . Consistent with the sensitivity of reduced P3 amplitude to risk for undersocialized alcoholism was the lack of a significant difference in the amplitudes of the sons of socialized alcoholics and nonalcoholics. To determine if P3 amplitude was related to alcohol and drug use, correlations were calculated between P3 size and the lifetime number of alcohol intoxications, the estimated alcohol consumed in the past year, and the number of times illicit drugs were used. The largest of these correlations was  $-.12$ , indicating that a little more than 1% of the variance in P3 size

was accounted for by substance use behavior. These correlation data are thus consistent with the notion that the primary determinant of P3 size in the sons of alcoholics is their father's socialization status.

Further, if P3 amplitude indexes risk for an undersocialized type of SA that is related to disinhibited tendencies, then we would expect that subjects who are high on our risk index would also produce relatively reduced P3 compared to those with lower scores. As Figure 14b illustrates, this is what we found. Again, we used planned contrasts to test our a priori hypotheses that (a) the boys with the most (three or more) indicators have smaller P3 amplitude than those with no indicators, (b) those with an intermediate number of indicators (scores between one and three inclusive) have smaller P3 than those with no indicators, and (c) the boys with the most indicators have smaller amplitudes than those with an intermediate number of indicators. As predicted, the boys with the highest index scores had significantly lower P3 amplitudes than those with a score of zero,  $t(466)$ , 2.41,  $p = .008$ . There were nonsignificant trends for the boys with an intermediate score to have significantly larger amplitudes than those with a zero score and for those participants with the highest scores to have smaller amplitudes than those with an intermediate risk index score.

### **A Model for the Development of SA**

As the foregoing review of MTFS findings and the research of others indicate, there is considerable support for a model of the development of SA that has multiple components. The model includes a genetic diathesis for an early-onset, undersocialized subtype of SA, which includes nicotine, alcohol, and illicit drug dependence, that is associated with behavioral undercontrol and disinhibition. A personality dimension related to behavioral disinhibition (MPQ constraint) underlies risk for the development of this undersocialized SA variant. Risk for undersocialized SA is manifest in a spectrum of related behavioral problems and disorders. Included in this spectrum are several childhood disorders, includ-

ing ADHD, CD, and ODD, and antisocial behavior, including delinquent or criminal acts, symptoms of AAB, and ASPD. CNS vulnerability to this spectrum of psychopathology may be indexed by psychophysiological measures tapping autonomic nervous system functioning sensitive to individual differences in inhibitory control. The model also posits that a common set of genes influences the personality trait of constraint, all the disorders that compose this spectrum, and the psychophysiological measures. These genes are transmitted from parents to their children and may be identified in their children by the presence of any of the spectrum disorders, low constraint, or psychophysiological anomalies associated with behavioral disinhibition. Our findings suggest that these genes convey a general predisposition for behavioral disinhibition rather than SA *per se*, and indicate that unshared environmental effects are important to the development of phenotypic characteristics associated with spectrum disorders, while both unidentified shared and unshared environmental effects are important to the development of SA.

Ultimately, as the fruits of the longitudinal aspect of the MTFs are realized, we will be able to test rigorously the various components of this model. This will include specifying the nature of the familial and nonfamilial influences on the development of SA, examination of the effects of gender, replication of the basic findings in the 11-year-old cohort when they are older, and specifying more fully the developmental pathway that leads ultimately to various SA outcomes.

The natural history of substance use and abuse has now been carefully described in several large-scale epidemiological studies (Bachman, Johnston, O'Malley, & Schulenberg, 1996; Kandel & Logan, 1984). The longitudinal design of the MTFs takes advantage of and builds on the findings from this earlier research. Early initiation of substance use, a powerful predictor of adult SA (Anthony & Helzer, 1991; Hawkins et al., 1997), will occur for many of the twins in our younger cohort between their intake (at age 11 years) and first follow-up (at age 14 years) assessment. Continuation and progression of substance

use as well as early indications of problem use can be expected to emerge between our age 14 years and age 17 years assessments (Clayton, 1992). By the time the twins reach their age 20 years assessment (the third follow-up of the younger cohort and the first follow-up of the older cohort), they will be at a life stage where illicit substance use is maximal and polysubstance abuse first emerges (Kandel, 1980). The use of tobacco and prescription drugs can be expected to peak in early adulthood (Chen & Kandel, 1995). We further expect that some of the twins will have ceased using illicit drugs by their age 23 years assessment and that many more will do so by age 26 years, by which ages they will have begun to assume the responsibilities of adulthood (Bachman, Wadsworth, O'Malley, Schulenberg, & Johnston, 1997). By the time they have reached their late 20s, we expect that all but the most hard-core abusers will have ceased illicit drug use, although late-onset cases of alcohol abuse, especially among women, can be expected to occur. Identifying the factors that distinguish these different outcomes and are involved in their etiology will be one of the major challenges we face. We have hypothesized that individual differences in various manifestations of behavioral disinhibition profoundly affect the life course of the development of SA such that those with multiple indicators of this underlying dimension are at greatest risk for early-onset, persistent SA. Our interest is in how inherited individual-level risk factors (such as indices of disinhibition derived from the personality, psychopathology, and psychophysiology research we have described here) interact with environmental factors (such as socialization experiences) to affect these life transitions.

As we begin to uncover clues about which children are at risk for developing SA, we also begin to offer information to policy makers as to where resources may be most effectively targeted. Our work and the work of others suggest that a serious and persistent form of SA may be foreshadowed by overt signs of disinhibition among those children at greatest familial risk for this type of SA. Efforts at the city, county, state, and federal government levels could be focused on providing training

and education for parents, teachers, and other agents of control in the community on how to evaluate whether a child is at risk for undersocialized SA and whether a child should be considered for a SA prevention program. Community-based programs would likely be best suited to the task of actually identifying and targeting children at risk for undersocialized SA. Teachers, coaches, school counselors, social workers and others who have contact with our youth are in the best position to work with parents in identifying children who, at an early age, are exhibiting conduct problems, signs of attention deficits or overactivity, oppositionality toward authority figures, and behavioral undercontrol. Further, resources at multiple levels could also help provide improved support, educational outreach, and parental training opportunities for high-risk families (e.g., those with an undersocialized, substance-abusing parent), perhaps even before the birth of children.

The effectiveness of such early prevention and intervention strategies may be profitably increased by empirical exploration of which strategies are maximally effective for different risk subgroups. Our model implies that

not all individuals who develop SA share the same risk factors. As already mentioned, our research suggests that one pathway to SA is partially mediated by genetic transmission of risk for a disinhibited syndrome. Different high-risk groups may respond best to different prevention programs. Outcome studies paying attention to differences in risk may help tailor programs for different risk groups. For example, improved prevention and intervention approaches for disruptive behavior disorders more broadly defined may help reduce the development of SA for these children. Furthermore, research on which environmental factors may play a buffering or protective role in stemming the development of undersocialized SA in those at risk for it may further inform such targeted approaches. We believe, as do probably most developmental psychopathologists, that well-conducted empirical outcome research, when informed by a scientific study of etiological factors, is the best bet for ameliorating the personal and societal consequences of SA. Finally, we stress that longitudinal, prospective, behavioral genetic research strategies add an important component to the later aspect of this endeavor.

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