Genotype-Environment Correlations and Interactions in the Etiology of Substance Abuse and Related Behaviors

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STATEMENT OF THE PROBLEM

Although the relevant behavioral genetic literature on substance abuse is limited, findings from this research, as well as from other behavioral genetic studies, strongly suggest that genetic factors exert some influence on substance abuse behavior. Consequently, although there is a need to carefully document the existence and strength of genetic influences, behavioral genetic research in this area needs to address how, rather than just whether, genetic factors influence substance abuse behavior.

Efforts at characterizing the mechanisms of genetic influence may proceed at multiple, complementary levels ranging from the molecular to the psychological. The approach described here focuses on traditional behavioral genetic methods to explicate what might be considered the ultimate step in the gene-to-behavior pathway: the transaction between genetically influenced psychological characteristics and experiential factors. It is argued that two behavioral genetic processes, genotype-environment correlation and interaction, may help in understanding how a complex and clearly experientially sensitive behavior like substance abuse might nonetheless be influenced by inherited factors. A behavioral genetic methodology relevant to identifying genotype-environment interactions and correlations is outlined.

BACKGROUND AND SIGNIFICANCE

The approach outlined in this proposal is based on two empirical conclusions derived from the research literature. Given the limited availability of empirical research in this area, these conclusions should be considered tentative and subject to further empirical confirmation. These conclusions are offered as premises that motivate this approach, rather than as empirically established truths.

Premise #1

Although the currently available evidence is limited, substance use and abuse, like most behavioral characteristics, are likely to be partially, albeit not entirely, genetically inherited.

In the past 20 years, as behavioral geneticists have turned their research efforts away from intellectual ability (the original focus of the nature-nurture debate) to other behavioral traits, they have been drawn towards a remarkable conclusion: Genetic factors appear to exert a pervasive influence on individual differences in virtually every aspect of behavior. Although the magnitude of the genetic effect certainly varies from one behavioral characteristic to the next, psychological characteristics ranging from brain waves and evoked potentials to personality self-ratings and social attitudes all appear to evidence some degree of genetic influence.

A direct and simple demonstration of the pervasive influence of genetic factors on human behavior is provided by Bouchard and colleagues' widely publicized study of twins reared apart (Bouchard et al. 1990). Since the study began in 1979, Bouchard and the research staff have located and assessed more than 120 twin pairs whose members had been separated at or near birth (average age at separation less than 6 months), and reared separately, for the most part without knowledge of one another's existence, until adulthood (average age at reunion approximately 30 years). Figure 1 summarizes findings from the Bouchard study for four separate domains of psychological functioning: cognitive ability, personality, interests, and social attitudes. The figure reports correlations, averaged across separate measures within each of the domains, among reared-apart identical twins (MZA) and reared-together identical twins (MZT), as well as the average reliability of the measures used. (For a discussion of methodology and description of findings in other domains, the reader is referred to Bouchard et al. 1990.) In this proposal, the authors focus only on the findings summarized in figure 1.

The substantial correlation in psychological functioning between the genetically identical yet separately reared MZA twins implicates the importance of genetic factors. Significantly, the findings from the Bouchard and colleagues' (1990) study replicate or have been replicated by other studies of separately reared twins (Pedersen et al. 1992) as well as by a large number of adoption studies and studies of reared-together twins (Plomin et al. 1990). The figure also demonstrates the importance

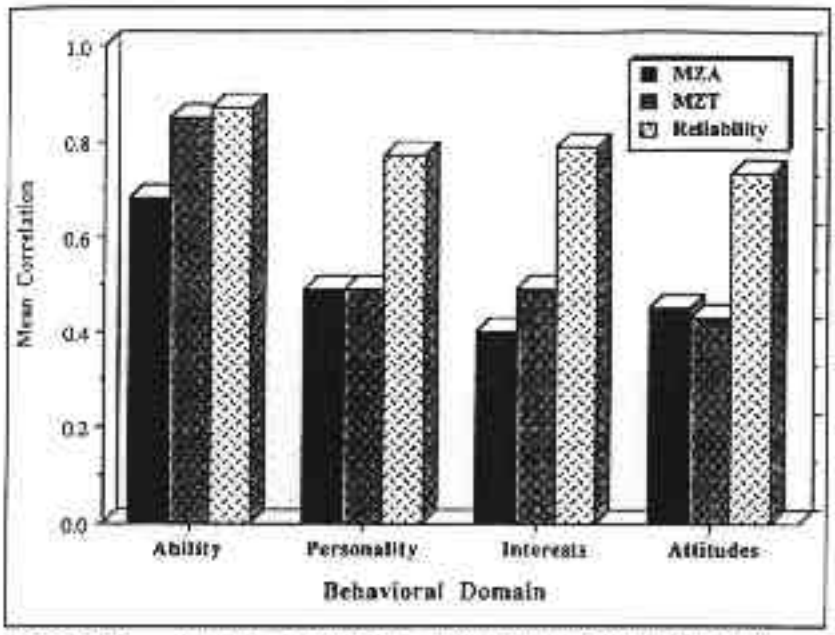

FIGURE 1. *Average correlation among reared-apart identical twins (MZA) and reared-together identical twins (MZT) and the average test-retest reliability in four behavioral domains.*

SOURCE: Adapted from Bouchard et al. 1990.

KEY: MZA = monozygotic reared apart; MZT = monozygotic reared together.

of environmental factors; the average MZA correlation is substantially less than the average test reliability in each of the four domains. However, as the average MZA and MZT correlations are approximately equal in at least three of the four domains, it appears that the relevant environmental factors are those that are not shared by reared-together relatives. This finding has also been replicated in a large number of studies of reared-together and reared-apart relatives (Plomin and Daniels 1987).

Given that the vast majority of psychological traits bear some relationship to intellectual ability, personality, or interests, the Bouchard study findings establish a strong a priori expectation that psychological traits in general, and substance use/abuse in particular, are at least partially inherited. This expectation has been repeatedly confirmed in the behavioral genetic literature, where virtually every

behavioral trait investigated appears to evidence some degree of genetic influence, and even finds support in the limited number of behavioral genetic studies on substance abuse. Pickens and colleagues (1991) reported monozygotic (MZ) twin concordance for drug abuse and/or dependence (other than alcohol or tobacco) as defined in the "Diagnostic and Statistical Manual of Mental Disorders," 3d. ed. (DSM-III) to be significantly higher among male MZ than male dizygotic (DZ) twins (concordance of 0.63 on N = 41 MZ pairs versus 0.44 on N=32 DZ pairs) and higher, but not significantly so, among female MZ as compared to female DZ twins (concordance of 0.22 on N = 19 MZ pairs versus 0.15 on N = 13 DZ pairs). Moreover, Cadoret and colleagues (1986) reported significantly higher rates of drug abuse in adulthood among the adopted-away biological offspring of parents with alcohol problems than among the adopted-away biological offspring of parents with no evidence of alcohol problems.

Implications of Premise #1. While the primary focus of much behavioral genetic research over the past 20 years has been to establish the existence of genetic influences on behavior, the accumulated weight of affirmative evidence has served to render most tests of the null hypothesis of no genetic influence relatively uninteresting. Thus, while it will be necessary, given the limited number of relevant studies in this area, to carefully document the existence and magnitude of genetic influences on drug use and abuse behavior, researchers can anticipate the likely result of such efforts: Substance use behavior, like virtually all other behavioral traits, will be shown to be partially, but not entirely, inherited. The chal-lenge to the present generation of behavioral genetics researchers is not so much in establishing whether genetic factors influence behavior, but rather how. As discussed below, two behavioral genetic processes, genotype-environment correlation and genotype-environment interaction, may prove particularly useful for moving beyond simple demonstrations of genetic effects to characterizing the nature of those effects and how those effects relate to the environmental factors known to influence substance abuse etiology.

Premise #2

Substance abuse exists within the context of a broad array of behaviors that include other indicators of undersocialization (e.g., delinquency), psychiatric disturbance (e.g., antisocial personality disorder (ASPD)), and temperamental/personality deviations (e.g., aggression).

In clinical settings, the polysubstance abuser is the norm rather than the exception; most substance abusers have also abused alcohol sometime in their lifetime, and cessation of one form of substance abuse is often followed rapidly by initiation of abuse of a different substance (Tarter and Mezzich 1992). The lack of substance abuse specificity also applies to other indicators of poor socialization. For example, precocious sexuality, gambling, delinquency in adolescence, and antisocial behavior in adulthood (Orford 1985) all occur more frequently among substance abusers than nonabusers. Substance abuse also coaggregates with a wide array of psychiatric illness, including depression and ASPD, both within individuals (Weiss 1992) as well as between individuals within the same family (Merikangas et al. 1992), suggesting that these disorders may share a common familial etiology.

There is also an extensive research literature relating substance abuse to specific personality characteristics (Sher 1991). Deviations along two broad dimensions of personality appear to be particularly relevant. The first dimension has been variously termed behavioral control, constraint, or behavioral dysregulation, and roughly corresponds to an individual's ability or willingness to inhibit behavior (Tarter and Mezzich 1992). Indicators of this first dimension include hyperactivity, impulsivity, and conduct disorder. The second robust personality correlate of substance abuse is negative emotionality (Pandina et al. 1992), or the tendency to experience negative mood states, indicators of which include neuroticism, anxiety, and alienation.

Figure 2 illustrates the association between substance use and personality factors using preliminary observations from an ongoing study of male adolescent twins. Self-reported substance use behavior of 17-year-old twins is classified as either light/abstinent (comprising the 51 percent of the total sample of 172 who reported no use of illicit substances over the past year), moderate (comprising the 38percent of the sample who reported limited use of one or two substances over the past year), or heavy (comprising the 11 percent of the sample who reported regular use of one or more illicit substances over the past year). In this study, personality is assessed through maternal and teacher report, and is thus not confounded with the self-reports used in making the substance use classification. Figure 2 gives the standardized effect sizes (i.e., mean difference in standard deviation units) comparing the light/abstinent and heavy groups for those personality ratings on which the groups differed significantly. As can be seen, the heavy substance-using twins were rated as more delinquent, more aggressive, higher on thrill seeking and

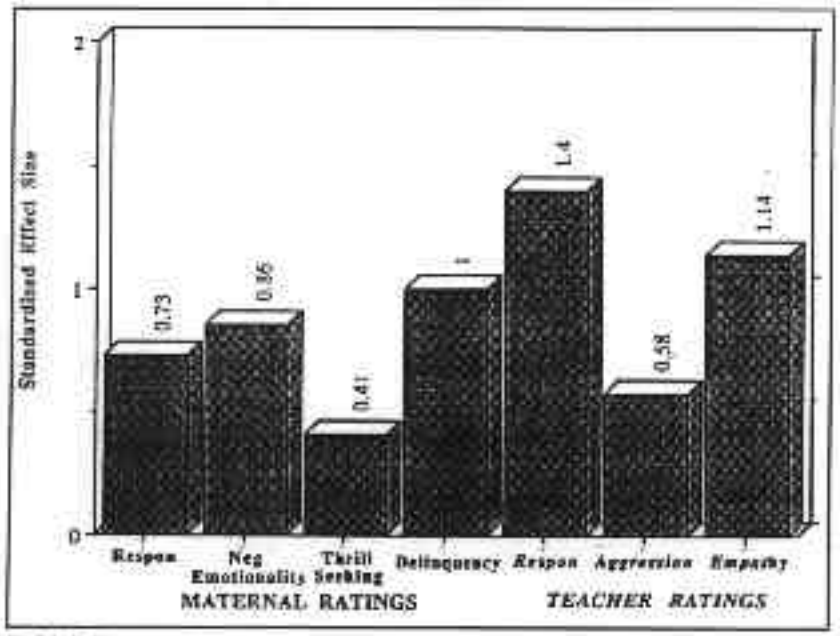

FIGURE 2. *Standardized effect sizes comparing heavy and abstinent/light substance-using male 17-year-old twins.*

NOTE: Effects sizes computed as mean difference divided by the standard deviation of the abstinent/light group. For responsibility (rated by mother and by teacher) and empathy dimensions, the heavy group scored lower on average than the abstinent/light group; for other dimensions, the heavy group scored higher. Effect sizes are reported only for dimensions for which there were significant group differences.

negative emotionality, and lower on empathy and responsibility, as compared to their nonsubstance-using peers (measures of positive emotionality failed to significantly differentiate the groups). The consistency and magnitude of the effects suggest that personality factors may play a fundamental role in the etiology of substance abuse.

Implications of Premise #2. The various correlates of substance abuse may help resolve the substantial clinical heterogeneity that characterizes this disorder. For example, alcohol researchers have long distinguished between two idealized pathways to alcoholism (Knight 1937; Sher 1991), and the correlations summarized above suggest that the same pathways may operate with substance abuse.

Included in the first group are those whose alcohol abuse appears to be a means of coping with psychological distress (i.e., the neurotic "self-medicators"). Included in the second group are those for whom alcohol abuse appears to be a manifestation of an underlying personality disorder (i.e., antisocial, thrill-seeking alcoholics). Cloninger (1987) has argued further that different biological pathways may underlie the expression of the two forms of alcoholism, with genetic factors playing a greater role among the antisocial as compared with the neurotic type. The Cloninger model provides a valuable conceptual framework for exploring genetic heterogeneity in other substance use disorders.

Findings from behavioral genetic research on other undersocialized conditions, and especially alcohol abuse, criminality, and delinquency, may help provide an important foundation for exploring the etiology of substance abuse. In particular, as reviewed below, behavioral genetic research indicates that the nature of environmental influence in sociali-zation disorders differs fundamentally from the nature of environmental influence with other psychological conditions.

Conceptual Framework

In considering the etiology of a complex behavioral characteristic like substance abuse, it is useful to distinguish proximal and distal determinants. The most powerful and immediate determinants of drug use behavior involve the context in which it occurs—substance availability, peer group pressure, prior reinforcement history, and so on. Genetic factors, to the extent they are relevant, would necessarily exert a remote and probabilistic influence on drug use behavior. The challenge to behavioral geneticists is to demonstrate how knowledge of a distal influence such as genetic factors can help researchers identify and understand the relevant proximal determinants of behavior.

Figure 3 (adapted from McClearn 1993) provides a useful heuristic model for conceptualizing the nature of genetic influence on behavior. The figure emphasizes two features of behavior that need to be considered in designing approaches aimed at identifying genetic etiology. First, the figure emphasizes the multiple levels of mediation, ranging from the molecular to the social, between primary gene product and an observed behavioral phenotype. Characterizing the gene-to-behavior pathway will

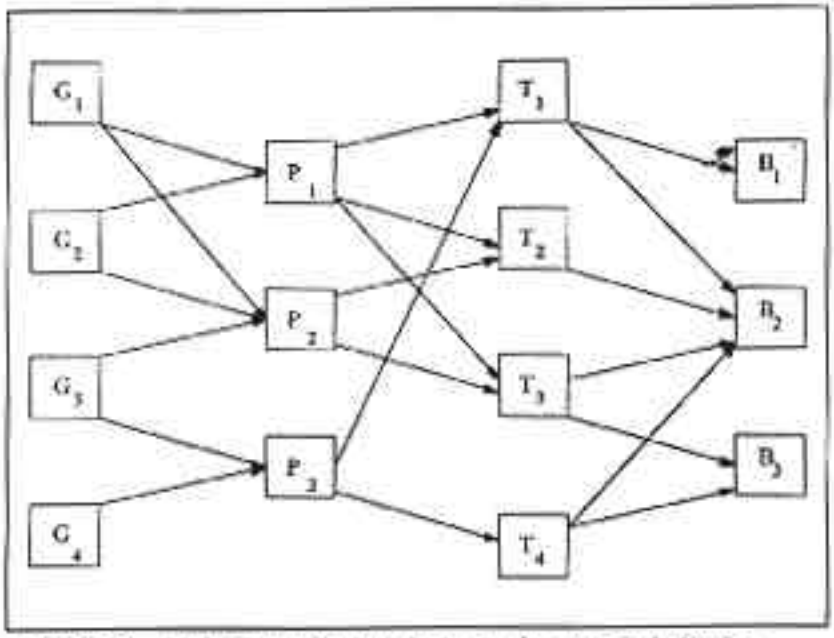

FIGURE 3. *Multiple mediating chains in the gene-to-behavior pathway.*

SOURCE: Adapted from McClearn 1993.

KEY: G = single gene effects; P = the effects of physiological systems; T = the effects of psychological traits; B = observable behaviors.

require multiple levels of analysis. Thus, although the association of single gene products with behavioral conditions is likely to provide major insight into the heterogeneity and etiology of behavioral disorders, it is highly unlikely that behavior will ever be reduced effectively and entirely to interactions among proteins. Alternatively, those who seek to characterize inherited behavior disorders through mediating, genetically influenced psychological and psychiatric conditions need to be aware of, and take into account, the molecular and neurochemical basis of these conditions.

The figure also serves to emphasize the fundamental influence of the environment on behavior. The further removed the phenotype is from the primary gene product, the greater the opportunity and thus the greater the likelihood for environmental effects. A comprehensive evaluation of environmental influence on substance abuse behavior

might parallel the multiple levels of genetic analysis: How do environmental factors moderate gene expression, neurochemical processes, and behavioral tendencies? Moreover, the existence of substantial environmental influence is likely to obscure attempts at identifying the molecular basis of behavior. One need only consider the general failure to find single gene effects on behavioral disorders such as schizophrenia (Sherrington et al. 1988), manic-depressive illness (Egeland et al. 1987), and alcoholism (Gelernter et al. 1993) to realize that application of molecular genetic methods to human behavior research is likely to proceed much more slowly than society has grown accustomed to after witnessing the remarkable discoveries made when this new method was used on classical genetic disorders such as cystic fibrosis and Huntington's disease. Indeed, without knowledge of the environmental mechanisms that produce incomplete penetrance and the resultant false negatives that vex genetic linkage studies, effective progress in identifying the genes that underlie behavior disorders may be altogether precluded.

The interest in this proposed study is in what might be considered the ultimate step in the gene-to-behavior pathway, that involving the trans-action between underlying, inherited psychological characteristics and the experiential determinants of substance abuse behavior. If contextual factors exert a strong proximal influence on substance abuse behavior, then distal genetic influences might usefully be characterized by how they increase an individual's chance of experiencing provocative situations (apossibility behavioral geneticists term "genotype-environment correlation"), how genetic factors cause different individuals to experience the same situation differently (a possibility behavioral geneticists term "genotype-environment interaction"), or both. Both possibilities can be explored using traditional behavioral genetic methods such as twin, adoption, and family studies.

The conceptual orientation and placement of substance abuse behavior within the broader context of undersocialized behaviors and conditions has led to the following three hypotheses about the behavioral genetics of substance abuse.

1. As there is increased opportunity for environmental influence in phenotypes far removed from the primary gene product, the strength of environmental influence is expected to be greater on socialization disorders such as drug abuse than on other behavioral characteristics more directly linked to physiological processes.

2. One mechanism of genetic influence involves the mediation of experiential risk factors by genetically inherited psychological conditions (i.e., genotype-environment correlation).

3. A second mechanism of genetic influence involves the inheritance of differential sensitivity to environmental influence (i.e., genotype-environment interaction).

GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO PHENOTYPIC VARIATION

Biometrical genetics is founded on the assumption that the variance (V) in a quantitative trait or phenotype, P, can be decomposed into components associated with genetic factors, G, shared environmental factors, C (environmental factors shared by and potentially contributing to the similarity among reared-together relatives, including socio-economic status of the rearing home, parental child-rearing strategies, etc.), and unshared environmental factors, E (i.e., environmental factors not shared and thus potentially contributing to the dissimilarity among, reared together relatives). That is,

$$VP = VG + VS + VE ,$$

where VP represents the total phenotypic variability, and VG, VS, and VE represent, respectively, the components of total phenotypic variance attributable to genetic, shared environmental, and unshared environ-mental factors. Alternatively, by dividing both sides of the equation by VP, one can decompose the phenotypic variance into proportions associated with genetic factors (h2 = VG/VP) (heritability)), shared environmental factors (c2=VS/VP), and unshared environmental factors (e2=VE/VP). Observations of twins and other reared-together and reared-apart relatives can be used to estimate the three relevant variance ratios and thus provide information on the relative contribution of genetic, shared, and unshared environmental factors to total phenotypic variability (Neale and Cardon 1992).

One of the more remarkable and provocative findings to emerge from recent behavioral genetic research is the observation that, while environmental factors exert a substantial influence on individual differences in virtually every psychological characteristic, the relevant environmental factors appear to be those that create differences rather than similarities among reared-together relatives (Plomin and Daniels

1987). That is, there exists a substantial body of research suggesting that the psychological similarity between two related individuals is largely independent of whether or not those individuals were reared in the same home by the same parents. However, there are two notable exceptions to this otherwise general conclusion on the absence of shared environmental effects on behavior. The first is intellectual ability and achievement (Thompson et al. 1991), and the second involves outcomes of the socialization process. With respect to the latter, for example, Mednick and colleagues (1984) reported that an adoptive parent background of criminality predicted likelihood of criminal registration in a sample of Danish adoptees. Cloninger and colleagues (1981) found rearing socioeconomic status to be related to alcohol abuse among Swedish adoptees. Of direct relevance to the present topic, Cadoret (1992) reported that adoptive parent divorce, sibling drug problem, or antisocial behavior among adoptive relatives were all related to drug abuse in a sample of Iowa adoptees.

The magnitude of shared environmental effects can be estimated from observations made in a classical twin study (i.e., the study of reared-together MZ and DZ twins). This can be illustrated from preliminary observations made in an ongoing study of male adolescent twins. Table 1 reports twin correlations derived from teacher ratings of 11-year-old male twins on three personality dimensions (aggression, responsibility, and extraversion), and three behavioral dimensions (inattention, hyperactivity, and conduct disorder). Under the standard biometrical model, the correlation (r) between MZ twins is rMZ = h2 + c2 while the correlation between DZ twins is rDZ = 1/2h2 + c2. Consequently, the parameters h2, c2, and e2 can be estimated from the observed twin variances and covariances using maximum likelihood methods described in Neale and Cardon (1992). These estimates (along with their standard errors) are also given in table 1.

Of greatest interest to the present discussion is the consistently substantial estimate associated with shared environmental effects. Extraversion, the dimension that is least related to socialization processes and thus of least relevance to substance abuse, is the dimension that evidences the highest degree of heritability and lowest degree of shared environmental effects, while conduct disorder (in this case specifically related to the rule-breaking behavior at school that can be rated by teachers) is the dimension that evidences the lowest degree of heritability and highest

TABLE 1. Twin intraclass correlations and variance components estimates for teacher ratings of 11-year-old male twins.

	Twin Correlation		Variance Component Estimate		
	MZ (N=111)	DZ (N=74)	h2	c2	e2
Behavioral Dimensions					
Inattention	0.74	0.56	0.38±0.15	0.37±0.15	0.25±0.04
Hyperactivity	0.72	0.48	0.20±0.17	0.49±0.17	0.31±0.04
Conduct Disorder	0.61	0.65	0b	0.63±0.05	0.37±0.05
Personality Dimensions					
Aggression	0.69	0.37	0.42±0.22	0.25±0.22	0.33±0.05
Responsibility	0.74	0.48	0.50±0.18	0.24±0.17	0.26±0.04
Extraversion	0.76	0.39	0.79±0.03	0b	0.21±0.03

KEY: h2 = heritability; c2 = proportion of variance due to shared environmental effects; e2=proportion of variance due to nonshared environmental effects; b = boundary solution, standard error is not estimable.

degree of shared environmental effects. In fact, the estimated heritability of the conduct disorder measure is 0.0, in apparent contradiction to the earlier claim that all behavioral traits evidence at least some degree of heritability. It is possible that this estimate may reflect a chance sampling fluctuation from a modest population value; other studies have reported significant but modest genetic influences on delinquency (Cadoret et al. 1983).

Although there is a clear need to replicate these preliminary observations in larger samples, the results summarized in table 1, as well as earlier twin adoption research, suggest that socialization behaviors may be less heritable and more environmentally influenced than other psychological characteristics. This is not an altogether unexpected result; much more is known about the environmental basis of rule-breaking behavior than about the conditions that promote extraversion among adolescents (Loeber and Dishion 1983). In any case, as the authors follow these 11year olds into early adulthood and the onset, in many cases, of drug use and abuse, they expect to find greater evidence of shared environ-mental effects than has been found in behavioral genetic studies of other behavioral characteristics and disorders.

Genotype-Environment Correlation

While individual differences in some behavioral traits may be traced relatively directly to nervous system processes, the behavioral complexity of the vast majority of psychological traits would seem to preclude easy reduction to basic neurophysiological processes. The size of an indi-vidual's vocabulary (Pedersen et al. 1992), one's interest in specific occupational pursuits (Moloney et al. 1991), and one's attitudes toward political ideologies (Martin et al. 1986) are all traits for which there is substantial evidence of heritability, yet none of these traits could be considered "hardwired." In each case, environmental factors—be they exposure to a rich assortment of words, specific political philosophies, or occupational models—appear to be the proximal determinants of behavior. The apparent contradiction of distal genetic with proximal environmental influence may find resolution in the proposition that genetic factors can influence complex psychological traits like interests and attitudes (or sub-stance abuse) by affecting the range of individual experience, a phenom-enon behavioral geneticists term "genotype-environment correlation" (Plomin et al. 1977; Scarr and McCartney 1983). In particular, individuals with different talents, temperaments, and physical characteristics (all traits that are, in part, genetically influenced) tend to evoke different reactions from parents, teachers, and peers (aprocess Scarr and McCartney call "evocative genotype-environment correlation"). When given a choice, these individuals may select experiences that are consistent with and reinforce their underlying genetically influenced abilities and interests (a process Scarr and McCartney call "active genotype-environment cor-relation"). In short, in a permissive society, the nature of individual experience is likely to reflect, in part, inherited behavioral tendencies and thus, perhaps ironically, represent a potential pathway for genetic influence.

To illustrate the mechanism of genotype-environment correlation and suggest how it might be applied to the etiology of substance use and abuse, consider what certainly is one of the strongest and most robust correlates of drug use behavior—peer group affiliation (Kandel and Andrews 1987). For the 11-year-old twins in the authors' study, teachers were asked to rate characteristics of the twins' peer groups in addition to rating the behavioral and personality dimensions mentioned above. When factor analyzed, these peer group ratings yielded two relatively distinct but correlated dimensions, positive peer group models (e.g., good students, involved in school activ-ities) and negative peer group models (e.g., rebellious, dangerous to be with).

Table 2 shows the twin correlations and the estimated variance components for these two dimensions of experience based on a preliminary sample of the 11-year-old twins. Although, as expected, there are sub-stantial shared environmental effects, there are also small (not estimated to be statistically significant) genetic influences on both peer group factors.

TABLE 2. Twin intraclass correlations and variance components estimates for teacher peer group ratings of 11-year-old male twins.

	Twin Correlation		Variance Component Estimate		
	MZ (N=93)	DZ (N=62)	h2	c2	e2
Positive peer models	0.75	0.62	0.17±0.15	0.57±0.15	0.26±0.04
Negative peer models	0.73	0.53	0.24±0.18	0.46±0.17	0.29±0.05

KEY: h2 = heritability; c2 = proportion of variance due to shared environmental effects; e2=proportion of variance due to nonshared environmental effects.

Insight into the process by which genetic factors might influence peer group affiliation is obtained by considering other correlates of peer group affiliation. As might be expected, there is a strong correlation between rated level of responsibility and exposure to negative peer group models ($r = -0.617$, $N = 310$, $p < 0.001$)—individuals rated as untrustworthy tend also to have friends who were rated as being problematic. Unlike standard cross-sectional research, however, research with twins provides additional information on the nature of phenotypic associations through analysis of cross-twin correlations (i.e., twin A's rated responsibility with twin B's negative peer models). The MZ twin cross-twin correlation between responsibility and negative peer group models ($r = -0.615$, $N=93$ pairs, $p< 0.001$) is substantially greater than the DZ cross-twin correlation ($r=-0.390$, $N = 62$ pairs, $p < 0.01$), implicating genetic mediation. Indeed, the MZ twin cross-twin correlation approximates the within-person correlation, indicating that MZ co-twin level of responsibility is as accurate a predictor of peer group affiliation as an individual's own level of responsibility. A genetic influence on peer group affiliation may reflect the effect of inherited psychological and behavioral characteristics on peer group choice.

An additional example from Lytton's (1990) recent analysis of parent and child effects in childhood conduct disorder illustrates how genotype-environment correlations can influence developmental processes. In reviewing the available evidence, Lytton makes a strong case for the proposition that much of the destructive and ineffectual parental behavior one sees associated with childhood conduct disorder may actually reflect the reactions of parents to the aggressive and defiant actions of their children. That is, child defiance is apt to be met, initially, with physical punishment and, if punishment proves ineffective, ultimately with neglect. In fact, both parental conflict and neglect are factors that characterize parent-child relationships in conduct-disordered families (Loeber and Stouthamer-Loeber 1986). Granting that ineffective parenting may represent reactions to offspring behavior, however, is not to conclude that these parental behaviors do not contribute to the etiology of childhood conduct disorder. In a series of investigations, Patterson (1982) has shown how evocative offspring behaviors can help establish "coercive cycles" that lead to an escalation of behavioral disturbance. Given the similarities between substance abuse and conduct disorder, the extensive literature relating experiential factors to substance abuse (Brook et al. 1992), and the likelihood that these critical experiences reflect individual choice to some extent, it will be important to determine the extent to which genetic influence on substance use and abuse is ultimately mediated by experiential factors.

Genotype-Environment Interactions

Most behavioral geneticists believe that inherited differences in sensitivity to environmental influence, a phenomenon they term genotype-environment interaction, represents a basic mechanism by which genes can influence behavior. Indeed, the dominant conceptual model of psychopathology is the diathesis-stress model, which emphasizes the integral and synergistic nature of genetic and environmental influences (Rende and Plomin 1992). That is, inherited factors (the diathesis) are hypothesized to establish individual levels of vulnerability that alone are not sufficient for the expression of behavioral pathology but rather depend in their expression upon the degree of environmental exposure (stress). In particular, the diathesis-stress model posits that environmental factors will be most critical among the biologically vulnerable, while those with low levels of biological vulnerability carry a low risk for the development of a behavioral disorder even when exposed to high levels of environmental provocation.

The most consistent support in the behavioral genetic literature for the existence of genotype-environment interactions has come from investigating socialization-related disorders (Cloninger et al. 1981 (alcoholism); Cadoret et al. 1983 (adolescent conduct disorder); and Mednick et al. 1984 (adult criminality)), which again motivates concern for the phenomenon in exploring the etiology of substance abuse. For example, not every child is swayed by negative peer group pressure, nor is every child likely to use drugs even when they are widely available. Inherited vulnerability may involve pharmacological responses that influence drug sensitivity as well as psychological characteristics that influence the likelihood of being affected by negative peer models.

DESIGN AND EXPERIMENTAL METHODS

The position and research from which this proposal is designed is that behavioral genetic research is appropriately directed not only at identi-fying specific gene products and characterizing the mediating role of inherited neurophysiological systems, but also at understanding how inherited factors combine with environmental effects to influence the development of complex behavioral characteristics such as substance abuse. In order to explore the joint influence of inherited and environ-mental factors in the etiology of substance abuse, the Minnesota Twin Family Study (MTFS) was initiated 5 years ago as a prospective behavioral genetic study of substance abuse. Details of this study are provided elsewhere (Iacono et al., this volume). This chapter focuses on those features of this ongoing study that are directly relevant to under-standing the relationship between genetic and environmental risk factors in the etiology of substance abuse.

Research Aims

The conceptual orientation motivated three testable hypotheses about the relationship between genetic and environmental influences, which are now specific research objectives.

1. Determine, using a twin-family study design, the relative contribution of genetic and environmental factors to the etiology of substance abuse and test the proposition that environmental factors exert a stronger influence (and genetic factors exert a weaker influence) on the development of substance abuse than on the

psychological and physiological factors that mediate the expression of this disorder.

2. Determine whether exposure to the environmental factors that increase the risk for substance abuse is associated, in part, with genetic factors (i.e., genotype-environment correlation).

3. Determine whether individual differences in susceptibility to the influence of the environmental risk are associated with inherited factors (i.e., genotype-environment interaction).

Sample Ascertainment and Structure

Ultimately the MTFS sample will be composed of 1,300 twin families. Families are selected such that: the twins in the family are either 11 or 17years old at time of assessment; approximately equal numbers of MZ, like-sex DZ, male and female twin pairs are included; and approximately 40 percent of the sample is designated as "high-risk" by virtue of having a biological parent who is alcoholic.

Each of these design features deserves comment. The cross-sectional composition of the sample is meant to capture adolescents at two key transition points in the etiology of substance abuse. At age 11, most individuals will have had limited or no direct experience with alcohol or prohibited substances. Consequently, the age 11 assessment will help to identify predictors of substance abuse initiation unconfounded by the consequences of substance use. Rates of substance use and antisocial behavior peak in late adolescence and then decline markedly in early adulthood. The purpose of the age 17 assessment is to identify factors that differentiate adolescent substance users who go on to have persistent adult problems from those whose substance use is transitory and primarily exploratory.

The study of a relatively large sample of identical and nonidentical twins and their parents represents one of the most powerful designs in behavioral genetics for resolving the separate influence of genetic and environmental factors. Because of the availability of national twin, adoption, and medical registers, most behavioral genetic research has been undertaken in the Scandinavian countries. Recently, however, MTFS researchers as well as others have shown how representative twin registers can be established in the United States (Lykken et al. 1990). In the present study, twin pairs are identified from records of twin births (birth records are public records in Minnesota) and the current status and location of the twins were determined using various

public sources (e.g.,telephone and reverse directories, school records). In the case of the adolescent twins in the MTFS, 92 percent of surviving twins have been located and approximately 80 percent of the twin families have been recruited to participate in a 1-day assessment. Consequently, this sample of 1,300 twin families is broadly representative of the population of Minnesota and includes twins who are being reared in especially challenging circumstances (e.g., single-parented, inner-city, on government assistance) as well as those from privileged backgrounds (e.g., intact family, low-crime community, high-income family).

The MTFS sample is selected to overrepresent families with alcoholic biological parents. Because most behavioral disorders, including substance abuse (Merikangas et al. 1992), aggregate in families, the offspring of affected parents constitute a group at relatively high risk for developing the disorder. Specifically, there is an extensive literature documenting that the offspring of alcoholics are more likely to suffer alcoholism, drug abuse, and psychiatric disorders and score higher on measures of delinquency and personality risk as compared with the general population (Sher 1991). Moreover, the strong phenotypic association between alcoholism and other substance abuse suggests that the offspring of alcoholics are a group that is at relatively high risk for developing substance abuse disorders.

Assessment

MTFS participants complete a day-long assessment protocol. An overview of the major components of this 8-hour assessment follows.

Systematic Assessment of Environmental Risk Factors. The assessment of environmental influences is organized around two broad categories that roughly correspond to the behavioral genetic decomposition of environmental variance into shared and unshared components. Familial environmental measures are those that aim to characterize the rearing home environment of adolescent participants and include assessment of family climate (e.g., Family Environment Scales, Moos and Moos 1981), specific parent-offspring relationships (e.g., that between rearing father and son), material resources of the home (e.g.,socioeconomic status, parental income), and parental attitudes about and models of substance abuse. Extrafamilial environmental measures are those that aim to identify formative experiences the adolescent twins have outside their rearing homes including peer group characteristics, life events, and nonfamilial social support.

Behavioral geneticists have been legitimately criticized for the simplicity of their approach to environmental assessment (Wachs 1992). Although some recent behavioral genetic research has begun to address this limitation (Plomin et al. 1994), all too often in behavioral genetic investigations the environment is conceptualized as nothing more than a residual, that which is left over after genetic effects have been partialled out. Comprehensive assessment of environmental risk is, however, critical to the general aim of understanding the relationship between inherited risk and environmental provocation. The assessment of environmental risk used in this study is based upon the substantial body of substance use/abuse research demon-strating, for example, that substance abusers are more likely to have poor relations with their parents than nonabusers (Coombs and Landsverk 1988), to come from families where behavioral control systems are incon-sistent and lax (Reich et al. 1988), and to be associated with peer groups where deviance is valued and reinforced (Kandel and Andrews 1987).

Multidimensional Assessment. Participants in the MTFS complete a comprehensive substance use and abuse assessment. The subjects are administered a structured psychiatric interview to assess comorbid diagnoses including depression and antisocial personality disorder (ASPD); undergo a comprehensive assessment of personality that includes multiple indicators of the two broad dimensions hypothesized to be most directly relevant to the etiology of substance abuse (i.e., negative emotionality and behavioral constraint) by self-report as well as by ratings by significant others (e.g., parents and teachers); complete an extensive psychophysio-logical battery (Iacono et al., this volume); and complete an assessment of academic achievement, aptitude, and commitment.

The need for a multidimensional approach to assessment is justified both by the oft-replicated observation that substance abuse characteristically exists within the context of other antisocial behaviors, and the need to move beyond the simple demonstration of genetic effects to a characterization of the nature of those effects.

Followup

There is a growing realization among behavioral scientists that many adult behavioral disorders are developmental; that is, while the disorder may be expressed primarily in adulthood, early signs may be manifest in adolescence or even preadolescence. For example, there is a strong association between adult drug use disorders and hyperactivity in child-hood (e.g., hyperactive boys are 10 times more likely than nonhyper-active boys to have a drug use disorder in early adulthood (Mannuzza et al. 1991)). Apart from the increased risk of adult behavioral disorder these early signs signal, they also implicate specific developmental pathways in the etiology of the disorder.

Mannuzza and colleagues (1991) showed that the association between childhood hyperactivity and adult substance abuse is mediated entirely by antisocial behavior, suggesting that the mechanism underlying the association may involve the relative difficulty of socializing hyperactive boys rather than, say, some untoward effect of early pharmacological treatment on later pill-taking behavior.

Adolescent participants will be followed into early adulthood in order to identify those twins who develop a chronic pattern of substance abuse. Participants are assessed annually with telephone interviews and through teacher ratings, and every 3 years complete an in-person assessment designed to coincide with major life transitions (e.g., from elementary to junior high, from high school to college or the job market).

Analytical Approaches

It is far beyond the scope of this document to comprehensively review developments in biometric genetics relevant to the aims of the MTFS. These developments (summarized in Neale and Cardon 1992) have provided behavioral genetic researchers with powerful analytical tools for exploring both univariate and multivariate hypotheses with twin and family data. Of relevance here is the development of methods to fit general univariate models to twin and family data, estimate the genetic and environmental components of phenotypic variance in those models, and test the goodness-of-fit of those models to the observed data.

Multivariate extensions of univariate models have been developed that allow investigation of genetic and environmental contributions to longitudinal stability and change and the covariances among a set of

measures. Most significantly, methods to explore the existence of both genotype-environment correlation and interaction with twin data are now available (Neale and Cardon 1992).

PUBLIC HEALTH SIGNIFICANCE

The consistent finding of genetic influences on most psychological characteristics suggests that, once the basic behavioral genetic studies are completed, substance abuse will also be shown to be affected by genetic factors. The likelihood of this result spurs consideration not only of whether genetic factors influence complex behavioral characters like substance abuse, but also of the mechanisms underlying that influence. Explicating these mechanisms may proceed along many levels of analysis; the approach proposed here is focused upon the transaction between inherited psychological traits and experience. In particular, it is argued that it will be difficult to understand the nature of inherited influence without simultaneously considering the nature of environmental influence. Genetic and environmental effects are likely to be synergistic (i.e., a genotype-environment interaction) and mutually interdependent (i.e., a genotype-environment correlation). This program of research is aimed at addressing these issues empirically.

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