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The Genetic Basis of Substance Use and Abuse[1]

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Significant genetic influences on use and misuse of alcohol, nicotine, and psychoactive substance use disorders (PSUD) have been clearly demonstrated. Nevertheless, environmental influences on these disorders are also important. Moreover, the mechanisms underlying the interplay between genes and environments are only now beginning to be understood. The purpose of the present chapter is to provide a brief overview of the behavioral genetic research on substance use and abuse disorders. In this chapter, I discuss results from univariate behavioral genetic studies of substance use and misuse, as well as behavioral genetic studies of comorbidity among different classes of substances, and behavioral genetic studies of comorbidity between substance use and other psychiatric disorders. In the second part of the chapter, I also discuss the potential heterogeneity in the different pathways that lead to substance use disorders, and studies of gene-environment interaction. This chapter focuses primarily on twin studies of illicit PSUD among adults.

Explanation of Terms Used in Behavioral Genetics

This chapter begins with a brief explanation of behavioral genetic terms and the assumptions behind the basic twin models. In behavioral genetic analyses,

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variation in any measured behavior or trait can be decomposed into variation due to three sources: genetic factors, shared environmental factors, and nonshared environmental factors. Generally, additive genetic factors (A) are the sole source of genetic influence, although nonadditive, or dominance genetic factors (D) are sometimes considered. Common, or shared environmental factors (C) are those environmental factors shared between two siblings in the same family, and that further serve to make individuals in a family similar to one another. Common shared environmental influences include socioeconomic status, family structure, community or school influences, and shared parent or peer influences. An important point to recognize is that in order to be a shared environmental influence, the environmental factor must have the same influence on behavior for both individuals. For example, the experience of parental divorce is an environmental factor that is *objectively* shared by two siblings in the same family. However, if one sibling responds to the parental divorce by 'good' behavior, such as throwing himself into his studies, and the other sibling responds by 'acting out' (e.g. skipping school and doing drugs), then parental divorce is not likely to be a subjective shared environmental influence for the cognitive or behavioral development of these two siblings. If divorce typically had dissimilar effects on all behaviors among siblings, it would count mostly as a nonshared environmental influence.

Nonshared environmental influences are any environmental influences that serve to make individuals dissimilar. Nonshared environmental influences can occur if exposure to the environment is not shared by siblings, such as effects due to birth order (e.g. differences in birth weight across twins), accidents, and different peer group experiences. Likewise, objectively 'shared' environmental factors that have different influences on behavior for individuals in the same family are also considered to be nonshared environmental factors, as discussed above. Finally, errors of measurement are also nonshared environmental influences, as errors are assumed to be uncorrelated across individuals.

Behavioral Genetic Methods

Because this chapter focuses primarily on results from twin studies, a brief description of the basic twin model (the ACE model) is provided. This model is shown in figure 1. The purpose of this method is to use observed correlations on any given measured behavior or trait (shown in fig. 1 by rectangles) across monozygotic (MZ, or identical) and dizygotic (DZ, or fraternal) twins to estimate the proportion of variation in a given behavior or trait that is due to underlying latent genetic (A), shared environmental (C) and nonshared

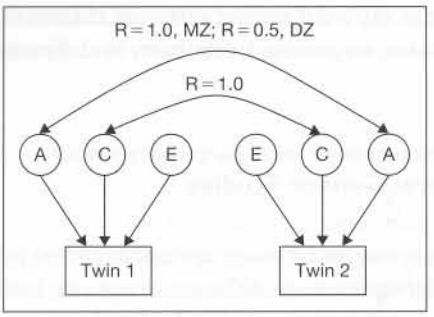

Fig. 1. The univariate ACE twin model.

environmental (E) factors (shown in fig. 1 as circles). MZ twins share >99% of their genes, and DZ twins, like full siblings, share on an average one-half of their segregating genes. This is indicated in figure 1 by the fact that A influences correlate 1.0 for MZ twins, but only 0.5 for DZ twins. Thus, if twin correlations for a measured behavior or trait (called a phenotype in behavioral genetic terminology) are higher for MZ twins than DZ twins, genetic influences are indicated. The proportion of variation in a given phenotype that is due to genetic influences is called the heritability. On the other hand, as can be seen in figure 1, shared environmental (C) factors are correlated 1.0 across twins, regardless of the twins' zygosity. Thus, if MZ and DZ twin correlations are equal in magnitude, then shared environmental factors are implicated. For MZ correlations that are greater than DZ correlations, but less than twice the magnitude of DZ correlations, both A and C influences are indicated. Finally, nonshared environmental factors (E) are those environmental influences that serve to make two individuals in the same family different. Thus, they do not contribute to twin resemblance (i.e. to twin correlations). This is illustrated in figure 1 by the fact that E influences are not correlated across twins. Estimates of E influence can be derived by subtracting the average MZ correlation from 1.0.

Although estimates of A, C, and E influences can be derived from a simple inspection of twin correlations as described above, behavioral geneticists typically rely on more sophisticated structural equation models such as those shown in figure 1. Structural equation modeling is particularly useful because (a) it can be applied to data with more than two sibling groups, (e.g. MZ twins, DZ twins, full siblings, and half siblings) and (b) these models can be used to determine the statistical significance of the genetic and environmental components (for details on structural equation modeling, consult Neale and Cardon [1]). Moreover, and perhaps most importantly, the basic univariate ACE model shown in figure 1 can be extended to more complex, factor-based multivariate analyses, as well as to models of gene-environment interaction, or to investigations of

whether heritability of a given phenotype is different among different classes of individuals (e.g. between males and females, or among twins born in different cohorts).

Results from Univariate Behavioral Genetic Studies

Univariate studies of illicit substance use and misuse are confounded by the frequent comorbidity of use of and dependence on different drugs (including alcohol and tobacco). In addition, research on individual substances is difficult because of the low prevalence and illegality of drug abuse, which further complicates efforts to recruit subjects and collect data. Thus, most studies have collapsed subjects across drug classes, combining different substance dependence diagnoses into a single phenotype of drug abuse/dependence.

Nevertheless, a number of univariate studies of substance use and abuse do exist. Perhaps the most research has been done on alcohol. Numerous adoption and twin studies have conclusively shown that genetic factors play a strong role in the etiology of alcohol abuse and dependence with most heritability estimates falling in the 50–60% range [2–8]. The liability to illicit PSUD also clearly aggregates in families, suggesting the importance of genetic and/or shared environmental factors [9–14].

Studies using data from three twin samples have examined illicit PSUD as assessed at personal interviews, two of which utilized population-based twin registries [15–19]. In these two population-based samples, genetic factors accounted for a substantial proportion of the variation in risk to develop abuse and dependence for cannabis, sedatives, stimulants, cocaine, hallucinogens, and opiates, with estimated heritabilities from these samples ranging from 25 to 79%, with most in the 55–75% range. The third sample, obtained through treatment settings, found estimates similar to those reported above among males for substance abuse or dependence (range = 0.57–0.78), but lower heritabilities for females [20]. However, this study was limited by small samples.

Finally, in a series of adoption samples, Cadoret and colleagues have produced consistent evidence for genetic etiologic factors in PSUD [21–24]. Thus, most twin and adoption studies agree that genetic factors play a moderate to strong role in the etiology of substance use and misuse. It should be noted, however, that 'rank orderings' of heritability estimates by different classes of substances varied across studies, due, at least in part, to the fact that the studies used slightly different measures of substances, and that confidence intervals around any given heritability estimate are quite wide, given the lack of power associated

with dichotomous data and low prevalence. Thus, the question of whether certain classes of substances are more heritable than others has not been resolved.

Comorbidity Across Substances

Given the high rates of comorbidity of substance use and abuse across different classes of drugs, it is interesting to consider whether the genetic factors that predispose an individual to PSUD are substance specific, or whether they confer a general liability to the use and misuse of any substance. Family and twin studies have found evidence for the specificity of familial aggregation of drug abuse, as well as a shared vulnerability to the abuse of different illicit and licit drugs. Although substance or drug-class-specific mechanisms of metabolism or pharmacologic action are sometimes found, there is still strong evidence for a single latent variable predisposing toward the abuse of illicit substances in general. For example, results from family studies of multiple substance use indicate that relatives of substance abusing probands have elevated risk for other forms of PSUD [12, 25], although, it should be noted that one study also showed some specificity in familial transmission [9]. However, one limitation of the family study design is that these studies cannot distinguish between family transmission due to shared genetic factors versus that which is due to shared environmental factors.

Thus, more conclusive evidence for genetic influence on comorbidity across substances comes from multivariate twin studies. Such studies have found significant genetic overlap between smoking and alcohol use/alcoholism [9, 26, 27]. In addition, at least two different twin studies have examined the genetic and environmental overlap across different classes of illicit drugs. In the first study, using data from 3,372 male twin pairs in the Vietnam Twin Registry, Tsuang et al. [28] found that a single genetic factor contributed to risk for addiction to all classes of drugs (i.e. marijuana, psychedelics, stimulants, sedatives, and opiates) along with additional modest substance-specific genetic factors. In this study, heritability estimates for the five individual drug categories ranged from 0.25 (psychedelics) to 0.44 (stimulants). The proportions of genetic variance in dependence for each drug that was shared with the common genetic vulnerability ranged from 30 (opiates) to 100% (psychedelics), suggesting that only certain classes of substances may show substance-specific genetic effects.

In a more recent study using our data, Kendler et al. [29] collected information from a sample of 1,196 male twin pairs who were part of the population-based Mid-Atlantic Twin Registry on lifetime history of use and DSM-IV-based criteria for abuse/dependence of cannabis, cocaine, hallucinogens, sedatives,

stimulants, and opiates. Heritability estimates for use ranged from 0.35 (cannabis) to 0.59 (sedatives and stimulants); those for abuse/dependence were higher for cocaine, cannabis, and hallucinogens, but lower for opiates, sedatives, and stimulants (range = 0.23–0.73). More importantly, multivariate structural equation model fitting revealed that genetic influences on risk for use and abuse of each class of drug were largely nonspecific: one common genetic factor accounted almost entirely for the risk for all six classes.

For use, the proportion of genetic variation that came from the common genetic factor ranged from 82% for hallucinogens to 100% for opiates. For abuse/dependence, 100% of the genetic influence on each substance came from the common genetic factor; i.e. there were no genetic influences that increased risk for one class of drugs that did not also increase risk for all others. Unique environmental experiences determined entirely whether one class of drugs was misused rather than another.

Results from these studies suggest that genetic influences on substance use and misuse operate primarily through genetic influence on a general tendency to use and abuse substances, and not from substance-specific genetic effects. This finding is somewhat surprising, given the fact that different classes of substances have very different pharmacological effects on the brain (e.g. the effects of sedatives versus the effects of stimulants). However, it should be cautioned that the prevalence of many of these individual substance classes is quite low. Thus, power to detect significant substance-specific effects may be limited. The addition of specific measured genotypes thought to affect metabolism and pharmacologic action on the brain into traditional behavioral genetic models may help to resolve this issue.

Figures 2 and 3 depict the phenotypic correlations among the different classes of drugs from the Kendler et al. [29] study as a function of overlapping genetic and environmental influences. Stated differently, figures 2 and 3 show the factors, genetic (A), shared environmental (C) and nonshared environmental (E), that explain *why* the use and abuse of one substance is associated with use and abuse of other substances. (In fig. 2, E1 and E2 refer to the fact that there were two different nonshared environmental factors that influenced covariation among use of different substances). There are three items of note in these figures. First, phenotypic correlations among different types of substances are quite high, ranging from 0.60 to 0.85 for the analysis of substance use, and from 0.67 to 0.85 for the analysis of substance abuse and dependence. Second, the majority of the correlations can be accounted for by genetic factors, indicating that the genes are the primary source of multiple substance use and misuse. This calls into question casual theories about the progression of substance use, such as Kandel's [30] Gateway Hypothesis, which posits that the use of tobacco, alcohol, and cannabis has a causal influence on risk to use other illicit

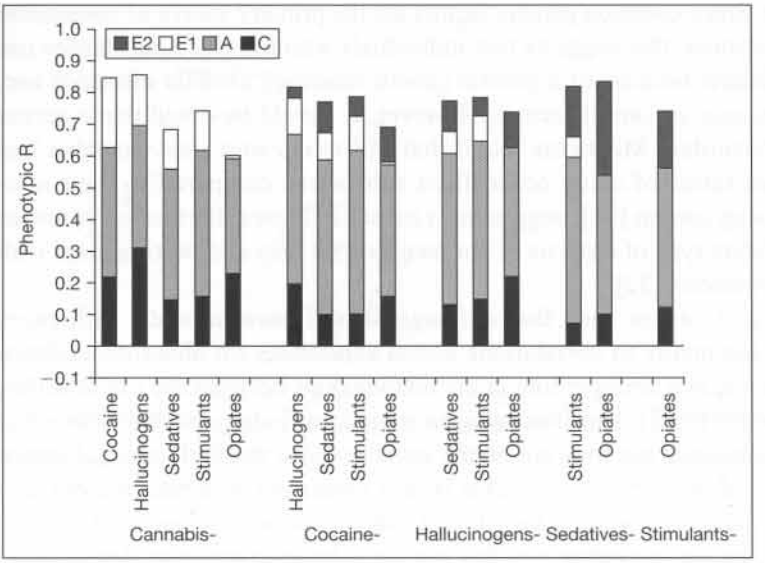

Fig. 2. Genetic and environmental contributions to phenotypic correlations between use of different substances.

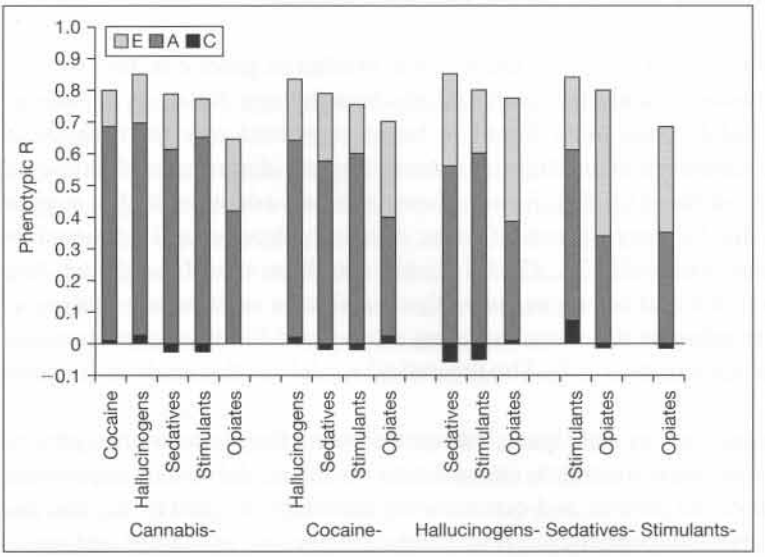

Fig. 3. Genetic and environmental contributions to phenotypic correlations between abuse/dependence of different substances.

substances. Since common genetic factors are the primary source of covariation across substances, this suggests that individuals who use illicit substances use these substances because of a general genetic tendency towards substance use, and not because of causal factors. However, it should be noted that a recent study of discordant MZ twins found that MZ twins who used cannabis had higher odds ratios of using other illicit substances compared to their non-cannabis using cotwin [31], suggesting a causal influence. Furthermore, results from a different type of analysis of our own data set may also be consistent with a casual hypothesis [32].

Finally, it can be seen that although shared environmental influences contribute minimally to correlations across substances for abuse/dependence (fig. 3), they play a stronger role in the relationships between the use of different substances (fig. 2). This illustrates the important finding that the factors that influence substance use may not be the same as those that influence substance misuse (e.g. abuse/dependence). This is also consistent with results from several univariate twin studies, which found that shared environmental influences are significant for substance use, but not for substance abuse or dependence, and that heritability estimates for abuse/dependence are typically higher than those for use [15–19].

Comorbidity with Other Psychiatric Illnesses

Another topic of interest is the possible overlap of genetic factors for substance use disorders and other forms of psychopathology. Relatives of individuals with PSUD have been found to be at increased risk for a range of psychiatric disorders, including depression, anxiety disorders and antisocial personality disorder [33, 34]. Results from twin and adoption studies suggest that this is due to shared genetic factors, although direct causal relationships may also play a role [22, 23, 35, 36]. Using data from the Mid-Atlantic Twin Registry, Kendler and colleagues recently completed a multivariate analysis of 9 different psychiatric illnesses, including alcohol and illicit psychoactive substance abuse/dependence [37]. The theoretical model for this analysis is shown in figure 4.

As can be seen in this figure, this model posits that there are two general classes of psychiatric disorders: internalizing disorders, defined by depression, anxiety, panic, and phobia, and externalizing disorders, defined by alcohol and substance abuse/dependence, child conduct disorder, and adult antisocial behavior. The model also allows for disorder-specific effects related to alcohol and substance misuse, presumably those related to physiological processing of substances in the brain. A multivariate extension of the basic ACE twin model

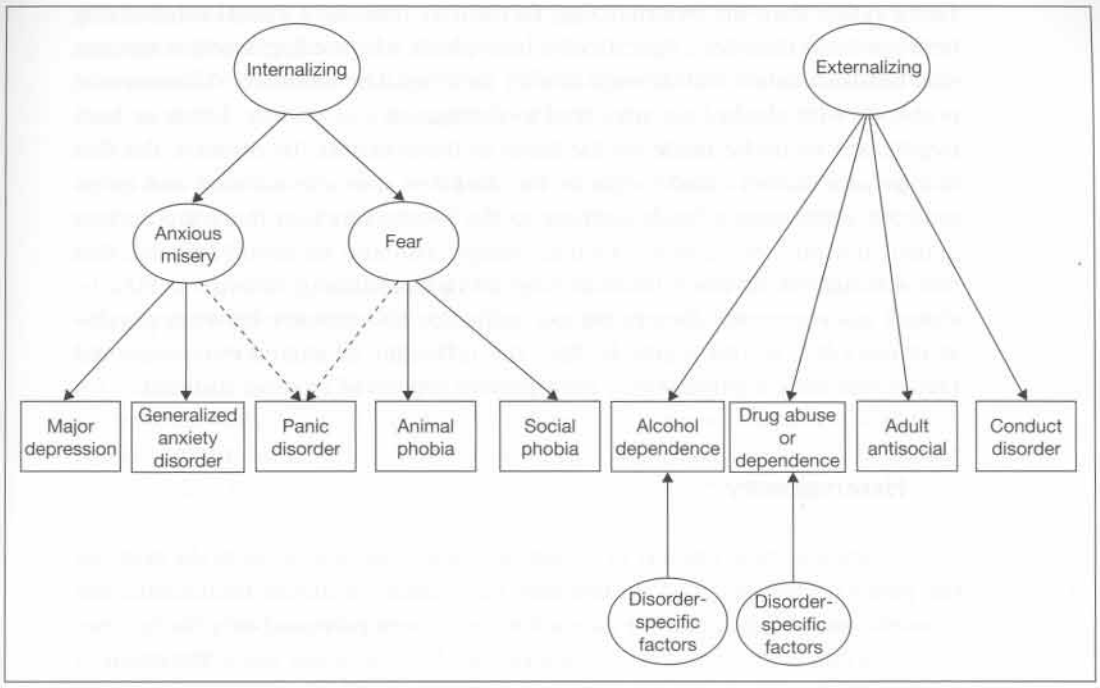

Fig. 4. Theoretical factor model for the multivariate analysis of 9 psychiatric diagnoses.

shown in figure 1 was applied to explain covariation among these 9 different outcomes [37]. Results were generally in support of the distinction between internalizing and externalizing. Specifically, the best fitting model allowed for both two genetic and two nonshared environmental factors. The first genetic factor loaded on depression, anxiety, and a composite factor composed of panic and phobia, but not on substance misuse or antisocial behavior. In contrast, the second genetic factor influenced the covariation between alcohol misuse, substance misuse, conduct disorder, and adult antisocial behavior. As expected, significant disorder-specific genetic effects were also found for alcohol and substance misuse.

The two nonshared environmental factors showed a roughly similar distinction: the first nonshared environmental factor loaded on depression, anxiety, and alcohol misuse, while the second nonshared environmental factor accounted for covariance between the two types of antisocial behavior. Illicit substance misuse did not load on either nonshared environmental factors; the effects of nonshared environment of illicit substance misuse were entirely disorder specific. The fact that alcohol misuse loads on the depression/anxiety

factor rather than the externalizing factor may indicate a causal relationship between these disorders. Specifically, individuals who are depressed or anxious may misuse alcohol in an attempt to allay their negative emotions. Alternatively, problems with alcohol use may lead to depression and anxiety. Either or both hypotheses could be made on the basis of these results. In contrast, the fact that genetic factors clearly separate the disorders into internalizing and externalizing components lends support to the hypothesis that there are certain genetically-influenced traits, such as neuroticism and sensation seeking, that can distinguish between internalizing and externalizing disorders. Finally, shared environmental factors did not influence comorbidity between psychiatric disorders in this study. In fact, the influence of shared environmental factors was only significant for retrospective reports of conduct disorder.

Heterogeneity

Of considerable interest to researchers and clinicians, alike is the fact that the pathways to substance misuse may vary among different individuals. For example, many typologies for alcoholism have been proposed over the last two centuries (for an historical review see Babor [38]). In recent years, the majority of research has focused on the binary typologies of Cloninger [39] and Babor et al. [40]. Although there are differences between the two typologies that are beyond the scope of this chapter, each typology broadly separates alcohol use that is accompanied by a history of past or present antisocial behavior from more 'pure' alcohol misuse. The antisocial form of substance use also generally has earlier onset. A large body of research has supported the existence of these typologies (for review see [38]), and adoption and family studies have confirmed that early-onset alcohol misuse accompanied by antisocial behavior is more heritable than 'pure' alcohol misuse [41–44].

Researchers are starting to apply similar typologies to the study of illicit psychoactive substance use. For example, Ball et al. [45] applied Babor's Type A/Type B typology to cocaine abusers and found that Type B cocaine abusers had more severe drug and alcohol use, higher rates of antisocial and other comorbid behaviors, and higher rates of premorbid risk factors compared to Type A cocaine abusers. Adoption studies by Cadoret and colleagues [22, 23] have also supported the existence of two genetic pathways to substance abuse, with one pathway going directly from biological risk for alcoholism to substance abuse/dependency, and the other pathway starting with antisocial behavior in the biological parent. For example, results from a recent study found that rates of substance use and abuse were elevated among adoptees whose biological parents have a history of *both* antisocial behavior and substance abuse

problems compared to adoptees whose biological parents have a history of only substance abuse problems or antisocial behavior ([24]; see also the chapter in this volume by Cadoret RJ for more information on the antisocial behavior-substance use pathways). These results suggest that one important pathway to substance use and misuse may occur through genetically-based factors related to antisocial behavior, such as behavioral disinhibition. In addition, there is evidence from twin studies that early-onset PSU may be more heritable than late-onset PSU [46].

Other aspects of heterogeneity that can be usefully explored include a consideration of differences in the importance of genetic and environmental factors for males versus females, for early-onset versus late-onset substance users, or for individuals born in different historical eras. The question of sex differences in the heritability of illicit psychoactive substance use and misuse is difficult to resolve, given the relatively low prevalence of substance use disorders among females, and the need for large sample sizes in twin and adoption studies in order to have enough power to detect significant genetic influence. Sex differences in alcohol use and misuse have been explored, however, and results are inconsistent. Some studies find higher heritability among males [47], whereas other studies find no differences (for review see [4, 48]). Clearly, more research is warranted.

Likewise, there is some evidence that the relative importance of genetic factors on variation in substance use and misuse may vary across birth cohort. Kaprio et al. [49] reported higher heritability estimates for alcohol use among twins born between 1951 and 1957 than among those born 1932–1950, especially among male twins. A twin study examining cohort changes in rates of regular tobacco use found that, among females, as the prevalence of smoking increased among more recent cohorts, the heritability of smoking also increased [50]. In our data from the Mid-Atlantic Twin Registry, we found evidence for a significant cohort effect on both mean level and sources of variation in conduct disorder [51]. Specifically, the prevalence of self-reported conduct disorder was increased among male twins born in more recent cohorts. As mean levels of conduct disorder increased, so did the magnitude of shared environmental factors (fig. 5). In contrast, as can be seen in figure 5, the magnitude of genetic and nonshared environmental factors remained stable over birth cohort. Thus, because heritability is calculated as the proportion of overall variation that is due to genetic factors, the heritability of conduct disorder decreased with more recent cohorts.

We have conducted a similar analysis of cohort effects using data on substance use and misuse, including the use and misuse of cannabis, cocaine, and any psychoactive substance [52]. Although there are interesting and significant trends in changes in prevalence of use across different cohorts, we could

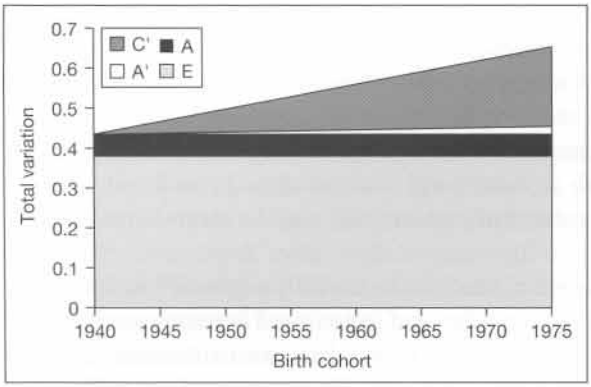

Fig. 5. Cohort effects on variation in conduct disorder.

find no evidence that the heritability of substance use and misuse varied across cohorts.

Gene-Environment and Environment-Environment Interactions

The final section of this chapter deals with the fact that it is clear that both genetic and environmental factors play an important role in the etiology of substance use and misuse. However, most of our behavioral genetic models treat these genetic and environmental influences as additive, or independent of one another. In reality, the interplay between genes and environment is likely to be more complex. For example, the above section describes how the heritability of substance use may vary across sex or cohort, suggesting that the importance of specific genetic and environmental factors may not be the same for all individuals. In addition, few studies have examined the moderation of genetic influences on illicit psychoactive substance use and misuse by a measure of environmental context.

In contrast, however, there is accumulating evidence that genetic influences on alcohol use and misuse vary by environmental context. In one study of adolescent Finnish twins, the heritability of alcohol use was higher among twins from urban versus rural environments [53]. In a follow-up study using the same data, investigators found that the heritability of alcohol use was higher in areas that had (a) greater numbers of young adults; (b) higher migration rates; and (c) higher alcohol sales [54]. In the AddHealth study of twins and siblings, the heritability of adolescent drinking varied by parental drinking behavior [55]. Specifically, heritability of alcohol use was higher among

adolescents whose parents drink than among adolescents whose parents did not drink. These findings suggest that levels of substance use among family members, peers, and community members, and the availability of substances may 'trigger' a latent genetic liability to substance use and misuse.

Relatedly, in a study of adult female Australian twins, heritability of alcohol consumption was higher among unmarried versus married twins [56]. In yet another study of Dutch twins, the heritability of alcohol use initiation was higher in twins who did not grow up in a religious environment, compared to those whose parents were religious [57]. These latter two studies suggest that certain protective factors may actually decrease a latent genetic liability to substance use and misuse.

Adoption samples have also suggested evidence for gene-environment interactions for alcoholism [2, 58] and for conduct disorder [59], a key risk factor for later substance use. Taken together, these findings of gene-environment interactions for alcohol use and misuse are in accord with the Bioecological Model [60], which hypothesizes that heritability of dysfunctional outcomes, such as substance use and misuse, should be enhanced in more disruptive environments, and/or in environments that promote substance use behaviors.

In addition to gene-environment interactions in the etiology of substance use disorders, there is evidence for environment-environment interactions. For example, among seventh graders in an urban, low income, predominantly African American school, the relationship between peer pressure to use drugs and actual drug use increased as a function of poor parenting [61]. In the AddHealth sample, the relationship between adolescent substance use and substance use by his or her peers was moderated by substance use measured at the school level, with higher adolescent-peer correlations in schools with higher average levels of substance use [62]. This latter result again suggests that substance availability is an important environmental 'trigger', this time for the selection of like-minded peers. Peer selection, in turn, may be partly influenced by genetic factors.

Finally, the success of recent molecular genetic studies of gene-environment interactions for antisocial behavior and depression using measured genotypes and measured environments [63, 64] indicates that a genetic 'propensity' towards psychopathology is not sufficient to cause a disorder. Instead, the pathways to psychiatric disease, including substance use disorders, are long and complex. Understanding the key environmental factors that may cause a genetically 'at-risk' individual to use substances will be an important tool for clinicians and those interested in prevention. Moreover, the ability to identify those who may be at risk for substance use disorders, due either to genetic and/or environmental risk factors, will be a valuable means of targeting specific prevention effects.

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