Gene–Environment Interaction Effects on Behavioral Variation and Risk of Complex Disorders: The Example of Alcoholism and Other Psychiatric Disorders

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There have been few replicated examples of genotype x environment interaction effects on behavioral variation or risk of psychiatric disorder. We review some of the factors that have made detection of genotype x environment interaction effects difficult, and show how genotype x shared environment interaction (GxSE) effects are commonly confounded with genetic parameters in data from twin pairs reared together. Historic data on twin pairs reared apart can in principle be used to estimate such GxSE effects, but have rarely been used for this purpose. We illustrate this using previously published data from the Swedish Adoption Twin Study of Aging (SATSA), which suggest that GxSE effects could account for as much as 25% of the total variance in risk of becoming a regular smoker. Since few separated twin pairs will be available for study in the future, we also consider methods for modifying variance components linkage analysis to allow for environmental interactions with linked loci.

The importance of gene–environment interaction effects (i.e. variation in the importance of genetic influences as a function of variation in environmental exposure) on behavioral variation and risk of psychiatric disorder remains controversial. Surprisingly, this is the case even for alcohol, tobacco and other drug use disorders, which show pronounced cohort differences in prevalence (e.g. Kessler et al., 1994; Robins & Regier, 1991), and which clearly require environmental exposure in the sense that they require ingestion of the abused substance. Here we explore reasons why such genotype x environment interaction effects have rarely been reported in the scientific literature.

The evidence for important genetic influences on risk of substance use disorders, however defined, is strong. For smoking, beginning in the late 1950s, and continuing until the present day, evidence from large sample national twin studies has accumulated that there are important genetic influences on risk of becoming a regular smoker, and to an even more pronounced degree, on the risk that an individual who has become a regular smoker will become a persistent smoker, still smoking at long-term follow-up (reviewed in Heath & Madden, 1995; Heath et al., 1998), or will become nicotine dependent (e.g. Kendler et al., 1999; True et al., 1999). For alcohol use, evidence from twin and adoption studies in samples of European ancestry supports important genetic influences on risk of alcohol dependence assessed by diagnostic interview or alcoholism identified through treatment or other official records (reviewed in Heath, 1995a; Heath, Bucholz et al., 1997), level of alcohol consumption in general population samples (Heath, 1995b), and experimentally determined measures such as subjective intoxication and static ataxia after a challenge dose of alcohol (Heath et al., 1999). Asian populations, where polymorphisms at genetic loci involved in the metabolism of alcohol (Aldehyde dehydrogenase (ALDH2) and alcohol dehydrogenase (ADH2)) are associated with differences in risk of alcohol dependence (e.g. Higuchi et al., 1994, 1996) provide a convincing demonstration both of genetic influences on level of alcohol consumption and risk of alcohol dependence, and of the routes (via effects on metabolism) by which such genetic influences can arise. Twin and adoption studies of illicit drug use have been much rarer and of more recent implementation, but both adoption data (e.g. Cadoret, 1992; Cadoret et al., 1995) and twin data (Tsuang et al., 1996) support important genetic influences on illicit drug abuse or dependence, with more recent twin studies providing evidence of genetic influences on use of (Tsuang et al., 1999; Kendler, Karkowski et al., 2000) and dependence on (Tsuang et al.,1998; Kendler, Karkowski et al., 2000; Lynskey et al., in press) specific drug classes (i.e. marijuana, opiates, cocaine or other stimulants).

More surprising than the consistent evidence for genetic influences on risk of substance use disorders is the absence of evidence for important environmental influences of parental alcoholism on risk of alcohol or drug dependence in the offspring generation. (Until the most recent

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cohorts, parental drug dependence will have been extremely rare, giving little opportunity to study environmental consequences of parental drug dependence). This is seen most clearly in the case of genetic studies on alcoholism, which have a more extensive literature than smoking or drug dependence. In the Danish adoption study, the first major adoption study of alcoholism, alcoholism in male adoptees, assessed as adults, who were the sons of alcoholic biologic parents, was significantly more common than in the adopted-away sons of control parents; and, furthermore, was no less common than alcoholism in the admittedly small number of sons raised by the same biologic alcoholic parents who had given another child up for adoption (Goodwin et al., 1974). In other words, having an alcoholic biologic parent predicted increased risk of alcohol dependence, regardless of the rearing history of the child. Likewise, in the much larger Stockholm adoption study of alcoholism (Cloninger et al., 1981), which used official reports of alcohol problems rather than direct interview assessment, alcoholism in adoptees was correlated with alcoholism in biologic but not in adoptive parents. Twin studies likewise have largely failed to find significant evidence for important family environmental influences on alcohol dependence risk (Heath, 1995a).

The apparent absence of environmental effects of parental alcoholism on risk of substance use disorders in the offspring generation would seem implausible given the high-risk environmental exposures seen in many families with an alcoholic parent or parents. For example, in diagnostic interview surveys of two different adult twin cohorts from the Australian twin panel, a reported history of parental alcoholism was associated with increased likelihood of reporting a history of childhood sexual abuse, in both women and men (Dinwiddie et al., 2000; Nelson et al., in press). History of childhood sexual abuse is in turn associated with increased risk of alcohol and other drug dependence as well as other psychiatric disorders (e.g. major depression, panic disorder, childhood conduct disorder: Kessler et al., 1997). Furthermore, it is unlikely that these associations can be explained by confounding effects since in twin pairs discordant for history of childhood sexual abuse, increased risk of psychopathology is consistently observed in the abused twins compared to their non-abused cotwins, albeit with this difference not always reaching statistical significance (Nelson et al., in press; Kendler, Bulik et al., 2000; Dinwiddie et al., 2000). Adult children of alcoholics report other high-risk exposures and adverse outcomes (e.g. Sher, 1991). So how is it possible that no consistent environmental influence of parental alcoholism has been observed in psychiatric genetic studies? In this paper, we seek to show that in order to address this question, we may need to reconsider the possible importance of genotype x environment interaction effects.

Theory and Methods

G X E interaction with no Genotyping, Unmeasured Environment

A number of pioneering publications in quantitative genetics addressed the analysis of genotype x environment (GxE) interaction in cases where there has been no genotyping (i.e. genetic effects must be inferred from the correlation between relatives), with notable contributions characterised by rigorous statistical treatment of GxE interaction by Jinks and Fulker (1970), and an extension of this work by Eaves et al., (1977). One important conclusion from this early work was that, even when no attempt was made to measure environmental exposure, under certain strong assumptions correlations between MZ and DZ twin pairs reared together and reared apart could be used to estimate the contributions to individual variation of additive and non-additive genetic effects, shared and non-shared environmental effects, and, of particular interest for this paper, genotype x shared environment interaction effects. The easiest way to understand this is to consider the contributions of these individual components to the correlations between relatives, as summarised in Table 1.

From genetic theory, we know that coefficients for the contributions of additive genetic and non-additive (dominance or epistatic) genetic effects to the correlation between MZ pairs, who share all of their genes in common, will be 1.0 and 1.0 (e.g. Jinks & Fulker, 1970); while for DZ pairs, who on average share 50% of their genes in common, and have a probability of 0.25 of sharing two genes identical by descent, that is, inherited from common ancestors, the corresponding coefficients will be 0.5 and 0.25 respectively.

Table 1

Contributions of Additive and Non-additive Genetic Effects and Shared and Non-shared Environmental Effects to the Correlations between MZ and DZ Twin Pairs Reared Together and Apart, When Genotype x Environment Interaction Effects are Present but Unmeasured

	Genetic Effects		Environmental Effects		Interaction Effects	
	Additive Genetic Variance	Non-additive Genetic Variance	Shared Environmental Variance	Non-shared Environmental Variance	Additive Genetic x Shared Environment	Additive Genetic x Non-shared Environment
MZ pairs reared together (MZT)	1	1	1	0	1	0
MZ pairs reared apart (MZA)	1	1	0	0	0	0
DZ pairs reared together (DZT)	0.5	0.25	1	0	0.5	0
DZ pairs reared apart (DZA)	0.5	0.25	0	0	0	0
Variance (all groups)	1	1	1	1	1	1

Note: interactions of non-additive genetic effects and environmental effects are ignored, but these effects are expected to be small. Genotype-environment correlation effects (e.g. because alcoholic parents both transmit high genetic risk to their offspring and expose them to high-risk environments) are also ignored, but would lead to higher variance in twin pairs reared together than in twin pairs reared apart.

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Under the hypothesis that MZ twin pairs reared together are no more highly correlated in their environmental exposures than DZ twin pairs reared together — an hypothesis that appears to be well-supported in the case of psychiatric phenotypes (Kendler et al., 1993) — the coefficients for the contribution of shared environmental effects to the resemblance of twin pairs reared together will be 1.0 and 1.0 for both MZ and DZ pairs reared together. In the absence of selective placement effects, the environmental correlation between twin pairs reared apart will be zero, and hence the corresponding coefficients 0 for both MZ and DZ pairs reared apart. Non-shared environmental effects will not contribute to twin pair resemblance, but will contribute to the total variance; and, in the case of separated twin pairs reared apart, this will also be true for environmental effects which do contribute to the resemblance of twin pairs reared together (hence in the absence of complications such as genotype–environment correlation, the total variance should not differ between twin pairs reared together and twin pairs reared apart: Eaves et al., 1977).

A general principle in statistics is that when we wish to model the multiplicative interaction between two components, the coefficient for the interaction term will be the product of the coefficients of the main effects of the individual components. Thus, as we can see from Table 1, the interaction between genetic effects and non-shared environmental effects will contribute to the total variance but not to the resemblance of twin pairs. In other words, this interaction term will be confounded with non-shared environmental effects (Eaves et al., 1977). In contrast, coefficients for the interaction between genetic effects, and shared family environmental effects, will be 1 and 0.5 for MZ and DZ twin pairs reared together, but 0 for both MZ and DZ twin pairs reared apart. If only data from MZ and DZ twin pairs reared together are available, the additive genetic variance, and the variance due to the interaction of additive genetic effects, and shared environmental effects, will be completely confounded, both terms having a coefficient of 1 for MZ pairs and 0.5 for DZ pairs. But if data on separated MZ and DZ twin pairs are also available, it will still be possible to estimate this interaction component as well additive (and possibly non-additive) genetic effects and shared and non-shared environmental effects. This possibility is illustrated in table 2, where we consider two hypothetical sets of parameter values, in the first scenario with additive genetic and shared environmental effects on twin pair resemblance, but no interaction effect; but in the second scenario with additive genetic, shared environmental, and additive genetic x shared environment interaction effects all contributing equally to the resemblance of twin pairs reared together.

GxE Interaction with no Genotyping, Measured Environmental Moderator

A second approach to the analysis of genotype x environment interaction effects, where measured genotype information is not available, avoids the need for separated twin data by assuming that it is possible to identify and measure major environmental 'modifiers' which interact with genetic effects (e.g. Heath, Neale et al., 1989; Neale & Cardon, 1992). Some applications from both adoption and twin studies have been published, although applications have been rare. In the context of adoption studies, this involves testing for an interaction between biologic parent characteristics (as an index of genetic predisposition) and adoptive parent or home environment characteristics (as an index of environmental risk-exposure) in predicting adoptee outcome. Cadoret and colleagues (Cadoret et al., 1996), for example, have reported that it is the co-occurrence of alcoholism in biologic parents and a history of psychiatric or behavioral disturbance in adoptive parents that predicts increased risk of depression in women. A similar approach has also been used in intact families in examining the interaction between presumed genetic risk (parental substance use disorders) and environmental exposure (high risk versus low risk peers) in predicting adolescent substance use at 14 (Legrand et al., 1999). In the study of twin pairs reared together, a test for genotype x environment interaction may be obtained by testing whether there is significantly greater heritability under high-risk than low-risk environmental exposure conditions, controlling for the average effect of the environmental risk-factor on the quantitative or categorical trait under

Table 2

Predicted Correlations Between Twin Pairs Reared Together and Apart for Two Hypothetical Traits, for Which Twin Pair Resemblance is Determined by Additive Genetic and Shared Environmental Effects only (Trait A) or Additive Genetic, Shared Environmental, and Genetic x Shared Environmental Effects (Trait B)

		Trait A	Trait B
Assumed population parameter values:			
Additive genetic variance		40%	20%
Shared environmental variance		20%	20%
Genetic x shared environment interaction variance		0%	20%
Non-shared environmental variance (including genetic x non-shared environment interaction variance)		40%	40%
Predicted twin pair correlations:			
Twin pairs reared together:	MZT	0.6	0.6
	DZT	0.4	0.4
Twin pairs reared apart:	MZA	0.4	0.2
	DZA	0.2	0.1

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investigation. Thus, in one study, there was evidence that genetic effects on alcohol consumption levels in women tended to become more important with age. However, when marital status was controlled for, there was also a significant genotype x marital status interaction effect, with more pronounced genetic influences on consumption levels seen in women without a marital or equivalent partner (Heath et al., 1989b). Other studies have found genotype x environment effects of religious upbringing on the personality construct of disinhibition (Boomsma et al., 1999) and on initiation of alcohol use (Koopmans et al., 1999), and of region of residence in Finland on patterns of adolescent alcohol use (Rose et al., 2001). Compared to the extensive behavioral genetic literature documenting genetic effects, however, reports of significant interaction effects have however been rare.

GxE Interaction with Measured Genotypes

The dissection of genotype x environment interaction effects will always be more powerful when both individual genetic risk-factors, and specific environmental risk measures, have been assessed. In contrast to research in cardiovascular genetics, which is rich in identified genetic polymorphisms and intervening phenotypes (e.g. Talmud & Humphries, 2001), psychiatric genetic research has been hindered by the absence of identified genes with major contributions to risk of disorder. Alcoholism in Japanese (or other Asians) has provided a notable exception, where a major genetic effect of the ALDH2 locus is observed. In a comparison of Japanese alcoholic patient series accumulated at three different time points, Higuchi et al., (1994) have documented an apparent genotype x environment interaction effect, with the protective effect associated with the heterozygous genotype becoming less pronounced in more recent patient series, a diminished protective effect that is attributed by the authors to increased social pressures for drinking after work experienced by Japanese males. (Unusually, for a psychiatric disorder, the low-risk homozygous genotype is almost completely protective, with very few alcoholics with that genotype identified in the world's literature: e.g. Higuchi et al., 1994).

In the absence of replicated findings of genetic polymorphisms associated with substantially increased or decreased risk of alcohol dependence in those of European ancestry, it may still be helpful to consider the implications for gene-mapping of genotype x environment interaction effects, for cases where genetic marker data are available. Analogous to the dissection of genotype x environment interaction using twin pairs reared together and apart, Table 3 (which for didactic purposes makes the simplifying assumption of complete linkage of a genetic marker and trait locus) summarises the contribution of a trait locus to variation in a quantitative trait for sibling pairs reared together and apart, stratified by number of alleles shared identical by descent at that locus. As in the case of data on MZ and DZ twin pairs reared together and apart, identification of full sib pairs reared together and apart who share 2, 1 or 0 genes identical by descent will allow for resolution of genotype x shared environment interaction effects associated with the trait locus. The practical application of such an approach is however likely to be limited to cases where very large sibships are being studied, because of the relatively low power of QTL linkage approaches except in large sibships (e.g. Sham et al., 2000). Whereas the frequency of separated twin pairs has declined substantially, the increasing frequency of parental divorce and irregular family structures has the consequence that, particularly in the case of large sibships, discovery of full siblings reared apart is likely to become a more realistic possibility.

Samples and Analyses

Separated twin data. Separated twin data are extremely rare and, because it is unusual in recent birth cohorts for twin pairs to be separated as children, typically limited to older cohorts (and thus uninformative about outcomes such as drug abuse). Where data on twin pairs reared together and apart are available, however, they have typically not been analysed in a way that would quantify the possible importance of genotype x shared environment interaction effects. The ideal study for this purpose is without doubt the Swedish Twin Register study of aging (the so-called SATSA study), which identified separated twin pairs and a subsample of twin pairs reared together from a national twin register. Pedersen and Kendler have presented data on regular smoking in this cohort (Kendler, Thornton et al., 2000), which we have reanalysed using standard maximum-likelihood model-fitting methods (including in the same analysis data from female like-sex and male like-sex twin pairs) to illustrate this point. In the

Table 3

Contribution of a Quantitative Trait Locus, and the Interaction of QT: and Shared Environmental Effects, to the Correlation between Full Sibling Pairs Reared Together and Apart

	IBD[a] at Trait Locus	Genetic Variance due to QTL	Shared Environment Effect	QTL x Shared Environment Interaction Effect
Full siblings reared together	2	1	1	1
	1	0.5	1	0.5
	0	0	1	0
Full siblings reared apart	2	1	0	0
	1	0.5	0	0
	0	0	0	0

Note: [a] Identity by descent

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reanalyses presented here, we ignore the apparent genotype x cohort interaction effects reported by Kendler et al., for these data. Models were fitted to summary contingency tables derived from the published data, using MX[1] with estimation of parameter estimates and their likelihood-based 95% confidence intervals under a model allowing for additive genetic, shared and non-shared environmental, and genetic x shared environmental effects.

Twin pairs reared together. To illustrate the analysis of GxE interaction effects in data from twin pairs reared together, using an environmental moderator variable, we have analysed data from the Australian twin panel 1981 cohort, a panel of twins who were first assessed by questionnaire in 1981, at which time they completed the Eysenck Personality Questionnaire (Heath & Martin, 1990), many of whom completed follow-up telephone diagnostic interviews in 1992–1994 (Heath et al., 1997b), which included an assessment of reported parental history of alcoholism (Slutske et al., 1996). We tested whether the heritability of the personality trait Neuroticism is increased in those with a reported history of alcoholism in one or both parents, using this as a gross index of shared environmental risk in the offspring generation. A positive parental history of alcoholism was inferred if at least one twin endorsed an item about parental alcohol-related problems "with health, family, job or police, or other problems" for either parent (Slutske et al., 1996). Analyses were limited to data from complete pairs who had participated in both the 1981 questionnaire survey and the follow-up diagnostic interview survey (910 MZF, 525 DZF, 386 MZM, 220 DZM, and 583 DZ unlike-sex pairs). Neuroticism scores were recoded as the proportion of items positively endorsed. Summary twin pair correlations were computed conditional on the presence or absence of a parental history of alcoholism. If suggestive evidence were found for genotype x environment interaction effects, models would be fitted to transformed scores by the method of maximum likelihood, with simultaneous modeling of (i) mean effects of parental alcoholism on Neuroticism scores (i.e. an effect on the expected mean for each twin pair), and (ii) moderating effects of parental alcoholism on genetic and/or environmental variances for Neuroticism, with the overall variance in Neuroticism scores modeled as VA(1+kP)+VD(1+kP)+VE(1+k'P), where VA, VD and VE are additive genetic, non-additive genetic and non-shared environmental variance components, P is a dummy variable coded 0 if there is no parental history of alcoholism, 1 otherwise; and k and k' are the coefficients for the multiplicative interaction terms, (VA x P) (also VD x P) and (VE x P) respectively. The goodness of fit of models with and without interaction terms would be compared by likelihood-ratio chi-square test, and 95% likelihood-based confidence intervals estimated.

Results

Separated Twin Pairs

Table 4 summarises results of reanalyses of the published SATSA regular smoking data from MZ and DZ twin pairs reared together and apart. While the GxSE interaction variance in this particular data-set is estimated at zero, from the associated 95% confidence interval we can say that it could account for almost a quarter of the total variance and remain undetected with the available sample sizes. As originally reported by Kendler et al., there is evidence for substantial heritability of regular smoking in this cohort (57%), and while the point estimate of shared environment effects is substantial (19%), it does not differ significantly from zero under this model.

Table 4

Estimated Genetic and Environmental Variances, and Genotype x Shared Environment Interaction Variance, for History of Regular Smoking in the SATSA Study (Data are Reanalysed from Kendler, Thornton et al. (2000)

	%	95% Confidence Interval
Additive genetic variance	57.4	36.6–75.0
Shared environmental variance	19.4	0.0–39.5
Genetic x shared environmental variance	0.0	0.0–23.4
Non-shared environmental variance	23.2	14.8–34.0

Table 5

Twin Correlations for Trait Neuroticism as a Function of Presence or Absence of History of Parental Alcoholism

	No Parental Alcoholism		Parental Alcoholism	
	N	*r*	*N*	*r*
MZ female pairs	694	0.51	216	0.48
DZ female pairs	386	0.20	139	0.28
MZ male pairs	296	0.47	90	0.52
DZ male pairs	166	0.19	54	0.03
DZ unlike-sex pairs	426	0.12	157	0.16

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Twin Pairs Reared Together

Among twins from pairs who both completed diagnostic telephone interviews and both had previously responded to the 1980–82 questionnaire mailing, approximately 19% (19.4% of women, 18.9% of men) reported a parental history of alcoholism. Neuroticism scores were only weakly predicted by parental alcoholism (R^2 = 0.01 in both genders; BETA = 0.049 in females, BETA = 0.057 in males). Twin correlations for Neuroticism differed remarkably little as a function of presence or absence of a parental history of alcoholism, giving no suggestion of a genotype x environment interaction effect: correlations were very similar in magnitude in both MZ groups, and while there was a trend for a higher correlation in DZ females from families with a parental history of alcoholism, the opposite trend was apparent for DZ male pairs.

Conclusions

While power to detect genotype x shared environment interaction effects will be an important limiting factor in cases where genetic effects must be inferred from the correlations between family members (e.g. MZ and DZ twin pairs), it is likely to be the case that application of appropriate statistical methods will uncover many more examples than are currently being reported in the literature. Reporting of confidence intervals for interaction components, even when non-significant, will at least give a better sense of the extent to which the existing literature may be overlooking potentially important genotype x environment interaction effects. In the reanalysis presented here of Swedish separated twin data, although a point estimate of zero was obtained, based on the estimated 95% confidence interval, the genotype x environment interaction component could account for as much as 25% of the total variance in risk of becoming a regular smoker. In the second example considered here, we tested for an interaction between genetic effects on the personality trait Neuroticism, and parental alcoholism used as an index of disturbed family environment, controlling for the average effect (genetic or environmental) of parental alcoholism on offspring Neuroticism. Despite evidence reviewed previously for an association between parental alcoholism and a variety of offspring environmental disturbances, we found no evidence for genotype x shared environment interaction effects on Neuroticism. The absence of such an effect for this personality trait is consistent with the consistency of findings from studies of twin pairs reared together, twin pairs reared apart, and adoption studies (e.g. Loehlin, 1992).

Analyses of genotype x environment interaction effects will always be more powerful when genotypes as well as environments can be measured. In the alcohol field, the identification of polymorphisms that affect alcohol metabolism that are associated with differences in alcohol dependence risk offers rich, although as yet underexploited, opportunities for studying such effects. As the number of specific genes that are confirmed to contribute to differences in alcohol or other substance dependence risk increases, a much more refined understanding of the interactions between measured genetic as well as measured environmental risk factors will become possible.

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Footnote

1 Neale, M.C., Bokes, S. M., Xie, G., & Maes, H. H. (1999). MX: Statistical Modelling available from Box 126 MCV, Richmond VA 23298: Department of Psychiatry. 5A Edition.

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