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GENE-ENVIRONMENT INTERPLAY IN RELATION TO EMOTIONAL AND BEHAVIORAL DISTURBANCE

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■ **Abstract** The conceptual and methodological issues involved in the study of gene-environment correlations (rGE) and interactions (GxE) are discussed in historical context. Quantitative genetic findings are considered with respect to rGE and GxE in relation to emotional and behavioral disturbance. Key conceptual and substantive implications are outlined in relation to both genetic and environmental risk mediation, with a brief note on evolutionary considerations.

CONTENTS

INTRODUCTION

Conceptually, gene-environment interactions (GxE) mean that there are genetically influenced individual differences in the sensitivity to specific environmental features (Eaves 1984, Mather & Jinks 1982). That they are likely to be present

is evident from the very consistent finding of huge individual differences in people's responses to all manner of stresses and adversities, however severe (see Rutter 2000b, 2001a). That might mean no more than that all behaviors are multifactorially determined, the heterogeneity reflecting the operation of other risk and protective factors, measured or unmeasured. However, that is only part of the explanation because experimental studies in humans and in animals have shown heterogeneity in response to experimentally induced risks even under highly controlled conditions (Petitto & Evans 1999). It may be assumed that organismic factors, which are genetically influenced, play a role in individual differential responsiveness. Gene-environment correlations (rGE) refer to genetic effects on individual differences in liability to exposure to particular environmental circumstances. The likelihood of their occurrence is suggested by the evidence that, through their behavior, people to some extent shape and select their environments (Rutter et al. 1997a). Thus, for example, children showing antisocial behavior are more likely, when adult, to experience seriously stressful life events and to lack social support (Rutter et al. 1995, 1998). A key issue concerns the role of genetic influences in these large individual differences in sensitivity and exposure to environmental influences—the topic of this chapter.

Behavior geneticists have long been aware of the potential importance of rGE and GxE because of their implications for the dynamic mechanisms involved in both genetic and environmental risks (see e.g., Cattell 1965, Eaves et al. 1977, Jinks & Fulker 1970, Plomin et al. 1977, Turkheimer & Gottesman 1996); moreover they play a prominent role in contemporary developmental conceptualizations (see e.g., Bronfenbrenner & Ceci 1994, Rutter et al. 1997a). Nevertheless, all too often, behavior genetic findings have been presented in terms of a partitioning of population variance into separate additive and nonadditive genetic components and shared and nonshared environmental effects, with a disregard for the possible role of rGE and GxE. That is now changing because of a greater realization of the crucial role of gene-environment interplay in risk and protective processes and because of advances in the means to study such interplay. In this chapter we review the methodological considerations, empirical findings, and conceptual implications, with special reference to emotional disturbance (anxiety and depression) and behavioral disorders (oppositional/defiant and antisocial behavior).

Before turning to the evidence on rGE and GxE, it is necessary to put two issues to rest. Although genetic research is far from free of problems, any dispassionate review of the evidence indicates that there are substantial genetic effects on psychopathology, including emotional and behavioral disturbance (Rutter et al. 1999a,b). Additionally, although it is true that much psychosocial research has failed to put environmental mediation hypotheses to the test in rigorous fashion, there are a range of effective strategies that do just that (Rutter et al. 2001), with findings that show the reality of important environmentally mediated risk effects (Rutter 2000a). Accordingly, it is possible to consider G-E interplay in the confidence that there are important gene (G) and environment (E) influences and, therefore, that their interplay is a legitimate topic of study. Moreover, there is

substantial epidemiological evidence to suggest that the interplay is likely to be important (Rutter et al. 1997a). Accordingly, an understanding of rGE and GxE should lead to more information on both environmental risk mechanisms and the processes by which genetic factors operate indirectly through effects on exposure to, and sensitivity to, the environment.

GENE-ENVIRONMENT INTERACTION

Conceptual and Statistical Background

Because, in order to analyze gene-environment interaction (GxE) satisfactorily, it is necessary to specify both the environmental influences and the individual genotypes, most of our understanding of the biology, until the advent of molecular genetics, stemmed from experimental work in plants and micro-organisms or from experimental breeding studies of animals (see e.g., Mather & Jinks 1982, McClearn et al. 2001).

The extensive range of studies of GxE in nonhuman species has established several principles (see e.g., Mackay 2001, Mather & Jinks 1982). First, although genetic control of sensitivity to the environment is widespread, the contribution of GxE to the overall population variance is typically smaller than the main effects of G and E even in controlled experiments using extreme environments. However, that does not apply to all biological processes or all genetic effects (see below).

Second, selection and breeding studies show that often different genes affect sensitivity to different features of the environment. There is little indication of a general GxE effect. Rather, there are genetically influenced sensitivities to specific environments, such sensitivities often applying only to minority subsets of the population (Rutter & Pickles 1991). It makes no sense to look for an overall interaction between genes and environments, and hence it is not surprising that "black box" analyses of anonymous G and E have usually failed to show GxE (Plomin et al. 1988).

Third, the genes that influence sensitivity to the environment may be quite different from those that bring about main effects. Moreover, there is both pleiotropy (one gene having diverse phenotypic effects) and polygeny (each phenotype being affected by more than one gene) (McClearn et al. 2001), in addition to genetic interactions, both between alleles within genes (dominance) and across genes (epistasis). The phenotypic expression of even single-gene disorders may be greatly affected by other (background) genes (Weatherall 1999). As a consequence, the detection of GxE is likely to be very difficult unless the individual genotype and the specific environment can be accurately measured. The task of understanding how a gene works in a larger environmental context is likely to prove considerably more difficult than simply finding a susceptibility gene for a multifactorial disorder or even determining what proteins it encodes (Wahlsten 2002).

Fourth, cross-fostering studies of animals genetically at risk (see e.g., Anisman et al. 1998) suggest that risks may be reduced by appropriate rearing—for example,

calm, nurturant, nonreactive mothers may provide a buffer against genetically influenced emotional hyper-reactivity (see Suomi 2000). The currently available data are too sparse for firm conclusions, but the experimental approach is clearly a fruitful one.

The seminal theoretical work on the quantitative study of GxE in humans was undertaken by Cattell (1965) some four decades ago when he sought to specify GxE statistically within his multiple abstract variance analysis (MAVA). An early formulation of a model for cultural inheritance also included GxE within the construct of genetic plasticity to the environment provided by parents (Cavalli-Sforza & Feldman 1973). Jinks & Fulker (1970), however, provided a more influential conceptual framework by considering the implications of GxE for second-degree statistics (variances and covariances) and higher-order moments (skewness, kurtosis, and means in relation to the variance) derived from clusters of family members. They showed that, if there were only additive genetic effects on sensitivity to the shared environment, GxE is confounded with main effects of G in the classical design of monozygotic and of dizygotic twins reared together (see also Molenaar et al. 1999). Help can be provided by the study of intrapair variance in separated twin pairs and by higher-order statistics that allow comparison of the effects of environments stratified by genotype (DeFries & Fulker 1985), or the converse if they are independent.

Several other statistical considerations are relevant.

1. There are several different types of gene-environment interaction that give rise to different models and different methods of testing (Kendler & Eaves 1986, Ottman 1996, Rutter & Pickles 1991).
2. It is a serious mistake to equate GxE with the statistical interaction term in a traditional multivariate analysis (see Eaves et al. 1977, Eaves 1984, Rutter 1983, Rutter & Pickles 1991). That is because, in some circumstances, GxE will be entirely absorbed in the main effect (see Rutter & Pickles 1991) and because a statistical interaction will only occur when there is a variation in both G and E (that will not apply, for example, to phenylketonuria when the risk substance is universally present in all ordinary diets or to hay fever, for which the exposure to pollens applies similarly to most people).
3. All forms of interaction (not just GxE) are extremely sensitive to scaling variations (see Brown et al. 1991, for an example with respect to two environmental risk factors). Variance-stabilizing or -normalizing transformations often eradicate apparent GxE (Mather & Jinks 1982). That does not necessarily mean that there was not genetically influenced sensitivity to the environment. There is no one "true" scale. There are parallel dangers of false positives and false negatives.
4. The statistical power for detecting GxE is much less than that for detecting main effects; accordingly, large samples are essential (Eaves et al. 1977; Wahlsten 1990, 1999).

5. Interactions may derive from multi-stage causal chain processes (Pickles 1993). Longitudinal data will be necessary to detect such forms of GxE. However, the interactive nature of a developmental process tends to become invisible after a sufficient time even under the most favorable circumstances (see Molenaar et al. 1999).
6. Although in theory, adoption designs are preferable to twin designs for the detection of GxE because they provide a "cleaner" separation of G and E, they have many disadvantages. That very separation (central to the design) results in there being very few individuals in the key cell that brings together G risk and E risk (see Bohman 1996, Cadoret et al. 1987). That means that the proportion of variance explained by GxE will be a major underestimate of the state of affairs in the general population in which that cell will be very much more common (Rutter 1987). Another problem is that adoptive families severely under-represent high-risk environments (because the choice of parents allowed to adopt excludes them as far as possible) (see Rutter et al. 1999a, 2001) and reflect a narrower range of environments (Stoolmiller 1999). An additional practical problem is that studies of adoptees often involve nonparticipation rates of over 50% (see Cadoret et al. 1995, Ge et al. 1996), raising the possibility of bias.
7. Unless the individual genotype can be specified (through DNA), GxE is difficult to assess satisfactorily in the presence of rGE. Expressed simply, that is because the high psychopathological risk in the G plus E cell could arise either because rGE means that individuals with high G also tend to have high E (with the consequence that the greatest risk, whether due to G or E, will appear to derive from their combination), or because there is a synergistic interaction between G and E (but see Eaves & Erkanli 2001 for a possible solution using Markov chain Monte Carlo methods within a Bayesian framework). Because from an evolutionary perspective both rGE and GxE reflect adaptive effects of G on E (Chadwick & Cardew 1996), it is quite likely in this circumstance that both rGE and GxE are operative, but statistically they cannot readily be differentiated. In multifactorial models it is also necessary to differentiate GxE interactions from ExE interactions (see Eaves & Eysenck 1977).

Molecular Genetic Findings in Internal Medicine

It is clear from all of these considerations that a greatly increased leverage on the study of GxE becomes possible once individual susceptibility genes can be identified, specific environmental risk factors can be accurately identified, and there is some testable hypothesis on a biologically plausible risk process. In the psychopathological arena the only much-studied example concerns the risk of Alzheimer's disease associated with the Apo-E-4 allele (Plassman & Breitner 1996, Rubinzstein 1995). Several GxE effects have been evident. Thus, Mayeux

et al. (1995) found that there was no increase in the risk for Alzheimer's disease associated with head injury in the absence of Apo-E-4, a twofold increase with Apo-E-4 alone but a 10-fold increase from the combination of Apo-E-4 and head injury. Similarly, Teasdale et al. (1997), in a 6-month follow-up of patients suffering a severe head injury, found that Apo-E-4 individuals were more than twice as likely to have a bad outcome. Yaffe et al. (2000) found that oestrogen use protected against cognitive decline in older women if they did not have Apo-E-4, but this was much less evident in those who were Apo-E-4 positive, reflecting GxE. More tentatively, there is a possible role for cholesterol in the GxE associated with Alzheimer's disease (Chandra & Pandav 1998).

Ischaemic heart disease provides a good parallel for what may be expected with mental disorders because in both cases causation is multifactorial, with many of the risk and protective factors operating dimensionally with large individual differences in susceptibility to them. Minihane et al. (2000) showed that the Apo-E-4 genotype influences responsiveness to fish oil supplementation effects on lipids. Birley et al. (1997) also used an experimental approach, finding that the lowering of LDL cholesterol associated with diet was greater in those with the NN blood group than in those with MN. Humphries et al. (2001) found that Apo-E-4 was a risk factor for ischaemic heart disease, but this mainly applied to smokers. Talmud et al. (2000) found that individuals with the D9N allele for lipoprotein lipase had a markedly increased risk of ischaemic heart disease when they smoked, the risk associated with smoking being much less in those who did not have this allele.

Other examples of GxE in internal medicine are evident in the marked individual differences in response to infections (Hill 1998, Knight et al. 1999) and to therapeutic medication (Evans & Relling 1999, Wolf et al. 2000). Reed (1985), in reviewing the extensive ethnic differences in alcohol use, abuse, and sensitivity, noted that the most striking difference concerned the lower alcoholism rate in Japanese as a consequence of high alcohol sensitivity of individuals who lack the ACDH-1 isozyme. This GxE effect, of course, concerns alcohol as the E feature. The application of molecular genetic methods to the study of GxE is only just beginning, but it is obvious that it is likely to be highly productive provided that the pathophysiological risk process can be identified in multifactorial disorders, allowing the testing of specific hypotheses on GxE instead of black box analyses of anonymous G and E (see Rutter & Pickles 1991).

Quantitative Genetic Studies of GxE on Psychopathology

Adoption studies have mainly been used to study GxE in antisocial behavior and substance abuse. Cadoret et al. (1983), in a study of 367 adoptees, found a significant GxE such that there was a negligible risk for adolescent antisocial behavior from a genetic factor alone (as crudely indexed by antisocial behavior in the biological parent), no effect from an adverse adoptive family environment alone, but a substantial effect when both were present. An earlier paper (Cadoret & Cain

1980) had shown that the effects of an adverse environment seemed to apply only to males, although biological risks were similar in the two sexes. Cadoret et al. (1995) studied 95 male and 102 female adoptees in Iowa. An adverse environment of upbringing was indexed by marital problems, divorce/separation, alcohol/drug problems or anxiety/depression or antisocial behavior in the adopting parents. Genetic risk was indexed by antisocial personality disorder in a biological parent. A significant GxE was found, with no effect of the adverse home environment on aggressivity and conduct disturbance in those without genetic risk but a substantial effect in its presence. Cadoret et al. (1996), in a study of the adult offspring of alcoholic biological parents, found that major depression in females was associated with an alcoholic genetic diathesis only when combined with disturbance in an adoptive parent. The findings in males were negative. Although the numbers in the G plus E cell were too small to show a statistically significant GxE, the pattern of an apparent GxE synergism was evident in studies by Cadoret et al. (1987) and Bohman (1996).

Crowe (1974) found that early institutional care was a risk factor for later antisocial behavior only when a genetic risk factor was present. Legrand et al. (1999) used the Minnesota Twin Family Study to examine the risks for substance use at 14 years associated with parental substance abuse/dependence (as an index of genetic risk) and affiliation with deviant peers (as an index of environmental risk). Both had significant effects, but there was also a significant interaction such that the familial risk effect was greater in the presence of high environmental risk. This implies GxE, but the design did not allow a clear differentiation of G and E.

Riggins-Caspers et al. (1999) used an entirely different putative E risk factor—the moderating effects of adoption agency disclosure of psychopathology in the biological parent. Significant GxE was found for both biological alcoholism and antisocial personality with respect to childhood aggression; the effects on adult antisocial personality in the offspring were much less striking. In other words, the genetic risk for childhood aggression that stemmed from parental psychopathology was increased if the adoptive parents knew about it. Putting the evidence together (but mindful of the limitations of adoptee studies and of the methodological considerations; see above), it may be concluded that the pointers all indicate a likely GxE effect with respect to antisocial behavior and substance use problems.

Twin designs have been employed in the only two studies of GxE with respect to emotional disturbance. Kendler et al. (1995) assessed putative genetic risk for major depression by regarding it as highest when there was an affected monozygotic (MZ) cotwin, lowest when there was an unaffected MZ cotwin, and intermediate with an affected dizygotic (DZ) cotwin (second highest) or an unaffected DZ cotwin (second lowest). The risk of onset of depression following a major life event was greatest in those at greatest genetic risk. This GxE effect implied that genetic factors operate in part by affecting the sensitivity of individuals to the depression-inducing effects of stressful life events. Silberg et al. (2001a), studying adolescent twin girls in the Virginia Twin Study of Adolescent Behavioral Development, used a different strategy. Attention was confined to life events (LE) not

showing rGE, with findings indicating a significant increase in heritability in the presence of LE, an increase entirely due to GxE. Phenotypic analyses showed no effect of LE on anxiety/depression in the absence of genetic risk, but a significant effect in its presence. Genetic factors, by contrast, did have a significant effect in the absence of LE, indicating either that there were direct as well as indirect effects on emotional disturbance or that the E risk stemmed from features other than the specific LE assessed.

Koeppen-Schomerus et al. (2000) used the same approach of comparing heritability according to the presence of identified specific environmental risk factors—in their case very premature birth and the associated obstetric and perinatal complications as they affected cognitive scores at age 2 years. The obstetric/perinatal effects were found to be environmentally mediated, but heritability of cognitive level was lowest in the presence of environmental risk, in other words, the opposite form of GxE to that found by anxiety/depression. Similarly, Rowe et al. (1999) in a study of a much older sample, found that the heritabilities for vocabulary IQ were significantly greater among the better educated than the less well educated. However, an earlier study showed only a marginal trend in the same direction (van den Oord & Rowe 1998).

The point of introducing these findings on a quite different phenotype is to underline the fact that GxE effects can be of several different kinds, each having rather different implications for the causal processes. In the case of both antisocial behavior/substance abuse and anxiety/depression, the implication is that an important part of the genetic effect is on sensitivity to key environmental influences (although part seems to operate more directly on the phenotype without the need for environmental mediation). There was little effect, however, from E in the absence of genetic risk. By contrast, in the case of cognitive level, genetic influences were maximal when E risk was low, and vice-versa. The implication is that the effects of G and E on IQ do not involve marked individual differences in sensitivity to the environment, but rather, represent somewhat different routes to the same outcome.

A rather different strategy for examining GxE has been to examine societal moderators either in terms of differences in some broad personal variable or in terms of cohort effects. Heath et al. (1989) noted that the heritability of alcohol consumption was much lower in married than unmarried women—both in younger and older age groups. In another Australian questionnaire study, Heath et al. (1998) showed that a married-like relationship also decreased the genetic effect on depression—again in both younger and older age groups. Boomsma et al. (1999) found that a religious upbringing was associated with a lower heritability for disinhibition; Koopmans et al. (1999) found the same with respect to alcohol use in females (but not in males). Dick and her colleagues (2001, Rose et al. 2001), in a Finnish twin sample, found that genetic influences on adolescent alcohol use were substantially greater in individuals living in areas with many young adults and high migration. They argued that communities characterized by more young adult role models and greater social mobility allowed for an increased expression of

genetic propensities that contributed to individual differences in adolescent drinking (although the community differences could reflect differences in genotypes or in genetic variance).

Several studies have examined cohort effects. Heath et al. (1985) found an increase in the heritability of educational attainment in Norway for males, but not females, over a time period in which educational opportunities became more widely available. Conversely, Kendler et al. (2000) found a rise over the twentieth century in the heritability of smoking in women but not men. Heath et al. (1993) found no differences across cohorts in the heritability of smoking initiation. Sellers et al. (1992) found a difference between earlier and later cohorts in the association between smoking and lung cancer (implying a GxE with respect to exposure to smoking). Silventoinen et al. (2000), in a Finnish study, found a marginal increase over time in the heritability of height (76% to 81%). The research strategy is potentially useful, but the results have been rather inconclusive.

On the other hand, large cohort changes in the level of a trait do have implications for the operation of rGE, as pointed out conceptually and mathematically by Dickens & Flynn (2001) in relation to the massive rise in IQ (some 20 points) that has been evident over the past half century (Flynn 2000). That has seemed to provide a paradox in that the cause has to be environmental, but such a large rise would seem to require an enormous environmental difference arising over a short period of time—the equivalent of, for instance, some three standard deviations, which seems implausible (Jensen 1973). Some form of multiplier must operate. Dickens & Flynn (2001) showed that rGE would have such a potentiating effect on E, and given the empirical demonstration of rGE, it seems reasonable to postulate that it may have been responsible. The argument is challenging because some behavior geneticists (e.g., Plomin 1994) have argued that rGE means that E effects have been overestimated in the past because they have included some genetic mediation (but see Eaves et al. 1977). Dickens & Flynn's (2001) model proposed that, although that will be the case to some extent, rGE enhances E and, hence, traditional partitioning of the variance tends to underestimate E. Their argument was directed at the rise in IQ, but it would seem to apply equally to the marked rise in emotional and behavioral disorders in young people that has occurred over the same period of time (Rutter & Smith 1995).

GENE-ENVIRONMENT CORRELATION

Conceptual and Statistical Background

As in the case of GxE, some of the basic insights on rGE stem from work in nonhuman species in which the environmental impact of parents on offspring may be manipulated through breeding and cross-fostering studies. The genes that influence the rearing environment provided by parents may not be the same as those that influence the offspring's phenotype directly (in which case there is no rGE

in relation to the phenotype). For example, human birth weight is almost exclusively determined by the shared environment. However, studies of the children of twins have shown that part of the environmental variation is the result of genetic differences in the mothers (Nance et al. 1983). It was this difference between rGE that did, and did not, contribute to the phenotype of the offspring that led Haley et al. (1981) to refer to "one character" and "two character" models of maternal genetic effects. This basic biometrical understanding of the genetic environment led to Eaves' (1976a,b) treatment of cultural inheritance and sibling interactions in humans.

Cattell (1965) made the important distinction between environments actively shaped by the individual and those brought about because genetically influenced behaviors may provoke particular environmental treatments, thus anticipating one aspect of the future taxonomy of rGE (Plomin et al. 1977). A major inhibition to the widespread acceptance of these early insights [in addition to some mathematical inconsistencies (Loehlin 1965)] was the lack of an explicit and parsimonious formulation of the roles of G and E in human families, a lack partially remedied by Jinks & Fulker's (1970) introduction of model-fitting methods. Among other things, they noted that passive rGE (meaning correlations between the overall family environment and genetic differences among families) may be expected to lead to differences in total variance between children raised by biological parents and those raised by adoptive parents. Subsequently, the rediscovery of Wright's work on path analysis by Morton and his coworkers (Rao et al. 1976) provided the first tractable model for the correlated effects of G and E in kinship data when there was one form of assortative mating (social homogamy). A variety of more general treatments of biological and cultural inheritance followed over the next two decades, allowing for different mechanisms of mate selection and sex differences in the expression of G and E differences (see e.g., Rice et al. 1978, Truett et al. 1994).

In their introduction of a taxonomy for rGE and GxE, Plomin et al. (1977) differentiated between passive, active, and evocative rGE. In the first, the relevant genotypes are those of the parents; their genetically influenced characteristics will help shape the environments they provide for their children. Plomin et al. (1977) pointed out that a direct measure of passive rGE was obtainable from a comparison of the correlations between family environment and child phenotype in adoptive and biological families (see also Plomin 1994). However, this is so only if the range of E, and particularly the proportion of high E risk environments, is similar in the two types of families. Subsequent data have made clear that this is rarely the case, at least with respect to the types of E related to the risk for emotional and behavioral psychopathology (Rutter et al. 1999a, 2001; Stoolmiller 1999).

The understanding of passive rGE involves five rather separate issues. First, there is the question of whether genetically influenced parental characteristics are associated with major differences in the environments of upbringing that they provide for their children. Epidemiological evidence is consistent in showing that there are strong associations between parental psychopathology and the family environments they provide (Murray & Cooper 1997, Rutter 1989).

Second, there is the rather different question of the strength of genetic influences on this association. That is best tackled through studies of adult twins in which the phenotype to be studied is the family environment they provide for their children, as indexed for example by the risk for marital breakdown (Jockin et al. 1996, McGue & Lykken 1992), coercive parenting (O'Connor et al. 1995), marital difficulties (Kendler et al. 1993), or parental overprotection and care (Pérusse et al. 1994)—most of which have been shown to be genetically influenced to some extent. Surprisingly little research on twins has focused on this important question.

Third, there is the question of which parental attribute mediates this genetic effect on the rearing environment. The issue directly parallels that considered in relation to LE (see below), but it has scarcely been addressed so far. Multivariate analyses of twin samples are needed to determine whether, for example, the genetic effects on divorce are primarily mediated through overt antisocial behavior, some temperamental feature (e.g., neuroticism, impulsivity, or sensations-seeking), lack of religiosity, anxiety/depression, or substance abuse. Jockin et al.'s (1996) study is one of the very few to examine some of these possibilities, with the finding that 30–40% of the heritability of divorce risk derived from genetic factors influencing personality.

Fourth, there is the question of the role of passive rGE in the risk mediation from the family environment to the child phenotype. The sampling bias in adoptee studies severely limits their use for this purpose. Offspring of twin designs (see Rutter et al. 2001) would be much more effective, but their use in this connection is only just beginning.

The fifth question concerns the parental mediator of the passive rGE as it applies to the child phenotype. Note that this is not the same as the third question discussed above. The difference is that it concerns the impact on the child behavioral phenotype rather than the family environment phenotype. The Colorado Adoption Project tackled the question with respect to the correlations between the Home Observation and Measurement of the Environment (HOME) and young children's Bayley scores (see Plomin 1994). It might be expected that parental IQ would be the obvious mediator, but surprisingly, that was not found to be the case, leaving open the need to explore other possibilities.

Active rGE differs from passive rGE in that the G concerns the child's genes rather than those of the parents (although obviously the former must come from the latter). It refers to the genetically influenced tendency for individuals to seek, create, or otherwise end up in particular kinds of environments. Longitudinal studies are consistent in showing quite strong associations between children's behavior and their environments in adult life (see e.g., Champion et al. 1995, Quinton et al. 1993, Robins 1966). Active rGE draws attention to the fact that these child behaviors are genetically influenced. Evocative rGE differs from active rGE only with respect to the fact that the E is defined in terms of other people's responses to the individual. In practice, of course, the two frequently overlap, in that people choose which sort of broader social environment they enter (peer group, leisure activity club, etc.) or the person with whom they develop a dyadic relationship (marriage partner, close

friend, etc.), but the ways in which they behave towards other people will evoke particular forms of responses from them.

Findings on Gene-Environment Correlations

Twin studies have examined the strength of genetic contributions to quite a wide range of environmental features that have been implicated in the causal mechanisms for emotional and behavioral psychopathology. Thus, Kendler et al. (1993), using the Virginia adult twin registry, found that genetic factors accounted for about 20% of the variance in life events (LE) over the past year; heritability was greater for personal events and negligible for network events (most of which are outside the influence of the individual). Kendler & Karkowski-Shuman (1997) used the MZ cotwin's history of illness as an index of genetic liability to major depression (see Kendler et al. 1995, as described above). This was associated with a significantly elevated risk for LEs; a genetic risk for alcoholism also predisposed to LEs in the personal domain. It was concluded that genes may influence the risk for psychopathology by causing individuals to place themselves in high-risk environments.

Plomin et al. (1990), in the Swedish adoption/twin study of aging (SATSA), found a 40% heritability, which was greatest for controllable LEs and least for uncontrollable ones. Using the same data set, Saudino et al. (1997) found a genetic effect only on controllable life events in women; there was no genetic effect in men. The genetic influence on LE seemed to be mediated by personality characteristics. Thapar & McGuffin (1996), in a Welsh study of children and adolescents, found a high ($\sim$0.60) heritability for self-rated LEs but a low one for LEs reported by parents. Genetic factors were also more influential for independent events in girls than boys, although the sample size was too small to test for the statistical significance of the sex difference. A later paper (Thapar et al. 1998) showed that the co-occurrence of LE and depression reflected genetic liability in part (but causal inferences are limited by the fact that the data came from the same informant). Silberg et al. (1999), using the Virginia Twin Study of Adolescent Behavioral Development, also found a significant genetic effect on the liability to life events. Most crucially, not only was the genetic liability to LE and depression shared, but also this was associated with the increasing heritability for depression in girls that is evident during the adolescent age period. Billig et al. (1996) found a heritability of 49% for nonindependent, nonfamily life events in late adolescence (using the Minnesota Twin Family Study), but little genetic component for other life events.

The topic of sex differences in relation to the effects of LEs on emotional disturbance, and the role of rGE, warrants further study. There is some evidence that stressful life events are more likely to lead to major depression in adult women than in men (Maciejewski et al. 2000), but the heritability for major depression seems to be greater in women than in men (Kendler et al. 2001). At first sight, these two findings seem contradictory in that the first appears to suggest that depression in women is largely environmentally determined, whereas the second appears to

indicate the reverse. The resolution of this paradox may lie in the effects of rGE and GxE in bringing about, during adolescence, a greater exposure to, and sensitivity to, LEs in females than was present in childhood (when the rates of depression in boys and girls are similar).

Genetic effects on individual differences in other life experiences have been shown for a wide range of features varying in their relevance for psychopathological risk. For example, Deater-Deckard et al. (1999), using the Colorado Adoption Project, found the heritability of parent ratings of negativity, inconsistency, and warmth to be 0.38, 0.04, and 0.26, respectively. Using data from the Non-Shared Environment in Adolescent Development project, Plomin et al. (1994) found an average heritability estimate of 0.27 for 18 composite measures of the family environment, with the genetic influence stronger on child-reported than on parent-reported variables. O'Connor et al. (1995), using the same study, found a nonsignificant heritability for mothers' anger, coercion, and transactional conflict towards adolescents; only fathers' transactional conflict showed significant heritability (27%). They noted, however, a serious problem with the Non-Shared Environment in Adolescent Development project, namely that the differences among sibling groups (full sib, half sib, and unrelated) were inconsistent with genetic theory. Also, the findings with respect to genetic influences on many variables differ according to whether attention is paid to twin comparisons or family comparison findings. Unfortunately, studies of divorced/remarried families inevitably involve troublesome confounds between genetic relatedness and family experiences.

Hur et al. (1996), using the Minnesota Twin Family Study, found heritability estimates for leisure activities that varied from 6% (religious activities) to 57% for intellectual activities. They concluded that interests, and engagement, in aptitude-based leisure time activities were affected by genetically influenced individual talents and abilities. In a study of adult twins using the parental bonding instrument, Pérusse et al. (1994) found heritabilities ranging from 19% (father overprotection) to 39% (mother care). Busjahn et al. (1999) showed that coping styles involved genetic influence. Deater-Deckard & O'Connor (2000), using a study of 125 same-sex preschool twins, found a heritability of 58% for dyadic mutuality. Brussoni et al. (2000) used a Canadian twin sample and found a heritability of 25–45% for a questionnaire measure of adult attachment. Elkins et al. (1997), using the Minnesota Twin Family Study, found significant heritabilities for parent-child conflict; heritabilities were higher at 17 years than at 11 years, possibly reflecting the fact that, as compared with younger children, older adolescents have more choice and impact on the nature of the relationships they have with their parents. Trumbetta & Gottesman (2000), using the Veterans Twin Registry, found that 31% of the variance in pair bonding could be attributed to nonadditive genetic factors, as could 22% of the variance in multiple mates. As already noted, there is a substantial genetic influence on divorce (McGue & Lykken 1992, Jockin et al. 1996). Using the Australian Twin Registry, Dunne et al. (1997) found that the genetic contribution to age at first sexual intercourse was greater in twins age 40 years or less than those aged 41–70 (49–72% vs 0–32%). The authors argued that, in the more laissez-faire

social climate that has operated in recent years, there is more opportunity for genetic influences to operate on choices in the initiation of sexual activity.

Although there is considerable diversity in both the quality of the data and of the samples, there can be no doubt that genetic influences play a substantial (albeit not a preponderant) role in influencing individual differences in the likelihood that people will encounter acute and chronic life events and experiences that carry important environmentally mediated risks for psychopathology. That conclusion has been resisted by many commentators on the grounds that it is clearly absurd to suppose that there could be a gene for divorce or for life events (Rose 1995, 1998). That is true, but the criticism completely missed the main point (Rutter 2001b). Most experiences that carry risks for psychopathology involve interpersonal interactions (Rutter 2000a). It must be assumed that people's own behavior will influence those interactions, and there will be genetic influences on that individual behavior. This does not entail genetic determinism because environmental factors have an equally strong (often stronger) impact on the same behaviors that shape or select experiences. Even more crucially, it is not deterministic because the fact that an adverse experience has to come about through genetically influenced individual behaviors does not mean that the effects on psychopathology are genetically mediated (Rutter et al. 1993) (see Environmental Risk Mediation, below).

CONCEPTUAL AND SUBSTANTIVE IMPLICATIONS

Environmental Risk Mediation

All psychologists are trained to appreciate that correlations do not necessarily mean causation. That is both because the statistical association does not indicate the direction of effect and because it could reflect the impact of some third variable. Bell (1968) raised the possibility that many supposed socialization effects reflected children's influence on other people, rather than the effects of rearing on children's behavior. Subsequent research (Bell & Chapman 1986, Rutter et al. 1997a) has confirmed the reality of these child effects. Evocative rGE considers the same point but with the additional consideration of the role of G in the child effect. Thus, both Ge et al. (1996) and O'Connor et al. (1998) found that antisocial behavior in the biological parent was associated with an increased likelihood that the adoptive parent would exert negative control, the main predicting mechanism being the child's own (genetically influenced) disruptive behavior. Without doubt, this evocative effect is important, but it should be noted that O'Connor et al. (1998) found that the association between adoptive parenting style and child behavior was almost as strong in the families in which the adopted child did not have an antisocial parent. The implication is that either there is also a true environmentally mediated socialization effect or the child effects derive from behavior that has been influenced by genetic or environmental risk factors unassociated with antisocial behavior in the biological parent.

There are three main implications of these findings for an understanding of environmental risk mediation. First, it should not be assumed that children's effects on other people necessarily mainly reflect G. Second, it is essential to identify the child behaviors mainly responsible for the evocative effects on other people and the proximal psychological processes by which these effects are mediated, especially in relation to the more extreme parental behaviors carrying high psychopathological risk. Third, with respect to developmental implications, longitudinal studies are needed to determine the ways in which child effects may provoke parental reactions that initiate either risk or protective bidirectional processes. Maccoby & Jacklin (1983) provided a lead, but there is a need for much more to be done. Cross-lagged phenotypic correlations in the context of cross-twin, cross trait analyses, over a developmental period of marked change are needed (see Silberg et al. 2001b for an example in relation to substance use and disruptive behavior).

With respect to third variable effects, behavior geneticists have tended to focus on the implications from evidence of substantial rGE that some effects attributed to environmental influences may, in reality, have been at least in part genetically mediated (Plomin & Bergeman 1991, Plomin 1994). The notion is not new; for example, Jones (1946) suggested that this was likely to be the case because the correlations between parenting features and child behavior were usually much stronger in biological than adoptive families.

However, rGE may reflect three very different mechanisms. First, measures of the environment (E) may be influenced by the characteristics of the person reporting on that environment. Insofar as that is the case, what is supposed to be E may, in reality, reflect the person (P), rather than E, with P being influenced in part by genetic (G) effects. This is the same issue as criterion contamination (i.e., the problem that arises when both the independent and dependent variables derive from reports by the same person). What is new is the recognition that this problem can arise even when the informants are different, if both share the same genes.

Second, the measure of E may be truly valid, but nevertheless, the individual differences in environmental risk exposure may be genetically influenced. Conventional behavior genetic analyses attribute the whole of this rGE to genetics, but this attribution misleadingly assumes that the origins of a risk factor and its mode of risk mediation are necessarily synonymous. The example of smoking clearly indicates that this assumption is false (Rutter et al. 1993). The origins of individual differences in smoking reflect both genetic factors (Silberg et al. 2001b), the availability of cigarettes, and sociocultural influences. However, the risk effects on osteoporosis, lung cancer, coronary artery disease, etc. involve mechanisms that are entirely separate—such as carbon monoxide, nicotine effects on blood vessels, and carcinogenic tars. As part of the broader topic of individual differences in environmental risk exposure (Rutter et al. 1995), it is important to determine the role of genetic influences, but it should not be assumed that this indicates the mechanism of risk mediation. Thus, O'Connor et al. (2000) found that, despite genetic influences on divorce, the effects of divorce on emotional disturbance (at least as measured by teacher report) were environmentally mediated in their study.

Third, the existence of rGE may mean that the associations between E and the psychopathological trait being studied are partially genetically, rather than environmentally, mediated. In other words, because parents pass on genes, as well as influence the circumstances of rearing, any correlation between the family environment and the individual attribute may derive from genetic (G) rather than environmental (E) mediation. Bivariate analyses of twin data, treating E as a phenotype and utilizing cross-trait as well as cross-twin correlations, provide the means of determining the extent of genetic mediation of effects associated with an E variable. Most studies have shown that G accounts for a substantial minority of the risk mediation but far from all of it (see e.g., Kendler et al. 1999, Neiderhiser et al. 1999, Pike et al. 1996, Plomin 1994, Reiss et al. 2000). The mediation that is truly E can be shown through the same approach, but it can also be determined by examining effects within MZ twin pairs (see e.g., Carbonneau et al. 2001, Kendler & Gardner 2001, Kendler et al. 1999, Rutter 2000c, Rutter et al. 2001, Silberg et al. 1999).

Both these methods concern child-specific environmental variables (although their effects can be mainly shared rather than nonshared) (see Pike et al. 1996, Rutter 2000c). Environmentally mediated risks that apply to both twins, but which involve rGE, can be examined by means of the extended twin-family design (see Meyer et al. 2000 for the rationale, the assumptions required, and the limitations). Environmentally mediated effects of early parental loss on the liability to alcoholism (Kendler et al. 1996) and of family maladaptation on antisocial behavior (Meyer et al. 2000) have been shown.

Six main implications for environmental risk mediation follow. First, there needs to be a greater focus on the origins of individual differences in environmental risk exposure, such differences being very large. Selection, shaping and evocative influences (whether or not genetically influenced) play a crucial role in the processes leading to variance in exposure, but societal effects are also important, as reflected in the operation of racial discrimination, availability of guns, local authority housing policies, availability of family planning, and schooling, to mention just a few examples.

Second, genetic designs (as well as other research strategies) have already shown the reality and importance of environmental mediation (see Rutter et al. 2001, Rutter 2000a). In addition, however, they have also shown violations of the equal environments assumption (EEA) that is fundamental to the use of the twin design for genetic purposes. That is to say, the same features (such as stressful life events or parental negativity) that show rGE also show associations within MZ pairs. This means that some of the effects attributed to G are in reality mediated by E. This is not a methodological artifact; rather, it reflects the reality of how G and E operate. Nevertheless, it does mean that twin studies of emotional and behavioral disturbance carry the danger of underestimating specific environmentally mediated risks (see Rutter et al. 2001, 1999a). That may seem surprising in that most reviews have concluded that there is no violation of EEA (see Kendler et al. 1994, Kendler & Gardner 1998).

Two points need to be made in that connection. (*a*) Most tests of EEA have considered features such as the amount of contact between the twins or whether or not they have been dressed alike. It is no surprise that these do not violate EEA because it is exceedingly unlikely that such features carry psychopathological risk. (*b*) EEA can be considered only in relation to specific phenotypes and not as a general phenomenon. Thus, the evidence does suggest violation of EEA with respect to emotional and behavioral disturbance but does not with respect to, for instance, autism or IQ because, so far, environmental risks that operate within MZ pairs have not been identified.

Third, the findings on GxE are challenging in their implication that environmentally mediated risks are slight in the absence of genetic risk. The findings so far are sparse, but they do all point in the same direction. They highlight the great need for further investigation of how environmental risks bring about their adverse effects and what they do to the organism. The findings on the importance of nature-nurture interplay clearly point to the need to study psychosocial risks within the context of biological processes, rather than outside it.

Fourth, several studies have findings that suggest possible differences between males and females in the interplay between nature and nurture (as well as differences between child reports and parent reports). Again, the data are too sparse for anything other than speculation, but it is possible that rGE and GxE may play a role in age-related changes in the sex ratio of some forms of psychopathology. Thus, for example, the data suggest that the rise of depression in adolescence, which is much greater in females than males, may be attributable to genetic effects on both exposure to, and sensitivity to, psychosocial risks, such effects being greater in women than men (Silberg et al. 1999, 2001a), perhaps because of the enhancing role of female sex hormones (see Angold et al. 1999, Petronis 2001).

Fifth, there is the intriguing suggestion from Dickens & Flynn's (2001) modeling of secular changes in IQ that rGE may play a crucial role in enhancing the effects of environmental influences so that they increase over time. There has been remarkably little systematic study of environmental influences on secular changes in rates of psychopathology in young people (Rutter & Smith 1995), and the implication is that twin studies of different cohorts could be informative, provided that they include good measures of the relevant E features.

Finally, rGE and GxE are relevant in relation to the claims that E tends to make siblings different rather than similar—the supposed preponderance of nonshared over shared effects (Plomin & Daniels 1987). These claims have been misleadingly overstated both because they have failed to take measurement error and temporal discontinuity into account (see Rutter et al. 1999a, 2001), because some commentators have misunderstood their meaning (see Turkheimer & Waldron 2000), and because some investigators have misrepresented their own findings (see Pike et al. 2000 in relation to Reiss et al. 2000). The message that it is important to examine child-specific environmental impact (Reiss et al. 1995) remains. However, there is the additional implication that it is necessary to examine how rGE and GxE result in family-wide E-risk features (such as divorce and conflict) impinging differently

on different children in the same family. Nonshared influences operate within, as well as outside, the family. Their study will require rather better measurement of environmental risks than has been the case in many behavior genetic studies undertaken so far.

Genetic Risk Mediation

There are four main implications of rGE and GxE for concepts of genetic risk mediation. First, in circumstances in which both are operative (as is the case with emotional and behavioral disturbance), a substantial proportion of the genetic influence will be indirect rather than direct. That is, the genes will be influential, in part, because they affect either exposure, or sensitivity, to the environment rather than because they bring about the psychopathological phenotype directly. Although it is not a necessary consequence, there is the implication that the risk processes may operate through dimensional attributes (such as temperament) rather than on any disorder as such. Thus, the genetic liability to ADHD could come about through effects on sensation-seeking or impulsivity (which predispose to ADHD) rather than through effects on ADHD itself. However, what is clear is that the main research need is not further studies of rGE adding to the list of E features that correlate with G, but rather more systematic investigation of which behaviors mediate the gene-environment connection both with respect to the environment and to the effects of this environment on the child phenotype (see discussion above of passive rGE).

Nevertheless, it is important not to overstate the case for indirect effects. It has proved much easier to identify effects of G in the absence of E risk, than the reverse. Of course, it may be that the measures of E were inadequate in quality or range of coverage. However, it is equally likely that there are important direct G effects that do not implicate the environment. We should not assume just one causal pathway, as highlighted by lessons in the study of comorbidity in internal medicine (Rutter 1997).

Second, up to now, most attention has been paid to active and evocative rGE, and it is apparent that there needs to be much more study of passive rGE. At least during the childhood years, it seems more influential than active or evocative rGE. However, in studying the effects of the environments of rearing that are shaped by genetically influenced parental phenotypes, it will be essential not to assume that effects will impinge equally on all the children in the family. A key research need is studies of the environmentally mediated impact of parental psychopathology with respect to both shared and nonshared effects.

Third, it should not be assumed that genetic risk mediation will operate in the same way with all psychological and psychopathological phenotypes. For example, the GxE found in two studies in relation to cognitive performance operated in the opposite direction to those found for emotional and behavioral disturbance. That is, not only was there no evidence of genetically influenced sensitivity to the environment, but genetic influences seem to be more influential in environmentally low risk homes. Of course, it is quite possible (indeed likely) that active (and

evocative) rGE was operative in such a way that genetically advantaged individuals were able to obtain advantaged environments. The study of rGE and GxE must cover the range of different ways in which they might operate, and also pay attention to both risk and protective processes.

Fourth, genetic evangelism and imperialism must temper its claims regarding the pervasive strength of genetic influences through an acceptance that the incorporation of rGE and GxE within the G term misrepresents the situation. Population variance cannot sensibly be partitioned into just G and E because an important minority of the variance has to be attributed to the joint action of G plus E. It should be mentioned, too, that the nongenetic component should not be assumed to be some specific environmental feature; stochastic features related to the probabilistic nature of developmental biological processes may also be operative (see Jensen 1997, Molenaar et al. 1993). However, in chiding some behavior geneticists for hiding the contribution of E within the G term, it is important to go on to accept that the important roles of rGE and GxE in risk and protective processes do indeed mean a centrality for genetic considerations in any study of causal mechanisms in psychopathology.

Evolutionary Considerations

The potential evolutionary importance of gene-environment correlations have been considered in fostering the intergenerational transmission of genes. Thus, Dawkins (1982, 1989) discussed the issue in terms of the concept of "extended phenotypes," reflecting the fact that genetic influences shape environmental selection in the direction of environments that are most adaptive for the individual genotype—a form of "niche-picking" (Scarr & McCartney 1983). There is no doubt that this does occur, but two main cautions need to be made. First, niche construction involves a two-way process that fundamentally changes the co-evolutionary dynamics between genetic evolution and cultural change (Odling-Smee 1996). Thus, nature-nurture interplay will also involve environmental effects on gene frequency. Two examples serve to illustrate the effect. (*a*) Genetic factors determine the ability of adults to synthesize lactose. In areas with long-established dairy farming, the great majority of adults are lactose-tolerant, whereas in other areas the reverse is the case (Bodmer & Cavalli-Sforza 1976, Durham 1991). The reliance on milk in the diet has favored lactose-tolerant genotypes. (*b*) Heterozygote status for thalassaemia constitutes a substantial protection against malaria. Accordingly, in malaria-endemic areas of Africa thalassaemia genotypes have become very common; conversely the frequency appears low in racially comparable individuals living in areas without malaria (although the data are limited and constrained by uncertainties over the ethnic comparability of populations), such as the United States (Davies & Brozovic 1989, Weatherall & Clegg 2001). Environmental features have had an important influence on the frequency of genes according to whether protection against malaria matters.

Second, the term niche-picking implies an active process that is governed by genes, as well as a process that is adaptive. That constitutes a misleading

oversimplification because (*a*) the selection of environments need not reflect an active process (Engfer et al. 1994); (*b*) effects on the environment stem from the characteristics of the organism, rather than of the genes (Lehrman 1965, Bateson & Martin 1999); and (*c*) evolutionary advantage applies strictly to reproduction and not to optimal social functioning (Bock et al. 2000). These caveats may be illustrated by considering the effects of antisocial behavior on environment, which are major with respect to a wide range of negative features spanning severely stressful life events, early marriage to a deviant spouse, disrupted close relationships, and lack of social support (Rutter et al. 1997b, 1998). Psychological studies show that environmental effects reflect the ways in which antisocial individuals engage with peers, impulsive actions that lack planning, and coercive interchanges with other people. The fact that they so frequently become parents while teenagers is as likely to reflect lack of planning as deliberate choice. The early childbearing may result in more live offspring, but this is not necessarily a social advantage in an urban industrialized society. Also, genetic influences account for only a moderate proportion of the population variance in the liability to antisocial behavior. In short, niche-picking is not necessarily socially adaptive and is not necessarily primarily driven by genes, although both will be the case in some instances.

CONCLUSION

It is abundantly clear that any adequate understanding of the processes involved in the initiation, remission, recurrence, and persistence of emotional and behavioral psychopathology will require identification of the varied mechanisms involved in rGE and GxE. In this chapter we have sought to summarize in succinct, nontechnical language, some of the conceptual and methodological issues that are involved, as well as the sparse array of empirical research findings. Brief mention was made of a few molecular genetic findings in internal medicine to illustrate the great potential of this field of research with respect to psychopathology (see Plomin & Crabbe 2000, Plomin & Rutter 1998, Rutter 2001b, Rutter & Plomin 1997), but progress will depend not only on the identification of susceptibility genes and their effects on proteins, but also on the use of molecular epidemiological methods of study of nature-nurture interplay (requiring the development of high quality E measures that can be used in very large samples and the development of hypotheses on plausible pathophysiological processes). The challenge can be met, but it will not be easy; the solutions will not come quickly; and success will depend on researchers honestly appreciating the conceptual and methodological hazards that will have to be addressed.

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CONTENTS