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Gene–environment interplay and psychopathology: multiple varieties but real effects

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Gene–environment interplay is a general term that covers several divergent concepts with different meanings and different implications. In this review, we evaluate research evidence on four varieties of gene–environment interplay. First, we consider epigenetic mechanisms by which environmental influences alter the effects of genes. Second, we focus on variations in heritability according to environmental circumstances. Third, we discuss what is known about gene–environment correlations. Finally, we assess concepts and findings on the interaction between specific identified genes and specific measured environmental risks. In order to provide an understanding of what may be involved in gene–environment interplay, we begin our presentation with a brief historical review of prevailing views about the role of genetic and environmental factors in the causation of mental disorders, and we provide a simplified account of some of the key features of how genes 'work'.

Over the past half-century there has been a series of changes in the generally prevailing views about the role of genetic and environmental factors in the causation of mental disorders. These changes were preceded in the first half of the 20th century (Cameron, 1956; Cairns, 1983; Kanner, 1959) by two background features. First, there was the introduction of unethical and abhorrent eugenic interventions on the misguided view of deterministic genetic effects (Devlin, Fienberg, Resnick, & Roeder, 1997). This background created a distrust of genetics in many behavioural scientists that has not entirely disappeared today despite genetic thinking and practice having changed completely (see Rutter, in press a). Second, there were numerous research reports of substantial associations between various environmental risk factors and the development of mental disorder. The Mental Hygiene movement placed great emphasis on the role of adverse experiences, both within and outside the family, in the predisposition to some mental disorders. This period also constituted the heyday of the influence of psychoanalysis on concepts and thinking in most of psychiatry and psychology. Behaviourism, led by the theorising of Pavlov and of Skinner, as well as by the advocacy of Watson, placed predominate emphasis on the power of learning with respect to all forms of behaviour.

Within the field of child mental health, Bowlby's (1951) review for the WHO of 'maternal deprivation', followed by Ainsworth's (1962) reassessment a decade or so later, put forward a powerful case for the overwhelming influence of children's upbringing in the early years. Reviews such as those by Pringle (1974) did much to popularise these views and foster their acceptance. Many people have seen this period, extending perhaps from the 1950s to early 1960s, as one of extreme environmentalism. There had been important genetic research (Shields, 1976; Slater & Cowie, 1971) but its impact on mainstream psychiatry and psychology was quite minor at that time. There was a 'token' acceptance that 'constitutional' factors played some role in individual differences but they were down-played and given little attention.

The next period, which might be considered to extend from the 1960s to the 1980s, was characterised by a major growth in behavioural and psychiatric genetics (Gottesman, 1991; Plomin, 1986). Twin studies continued to show important genetic influences on most types of psychopathology, but it was the availability of evidence from adoption studies that probably played the major role in forcing people to accept the reality of genetic influences (see Kendler, Gruenberg, & Kinney, 1994). By the end of the 1980s, most reviews of the field accepted the importance of genetic influences on variations in the individual liability to mental disorders (Rutter et al., 1990a, 1990b). This came about partly through improvement in the quality of twin designs, partly through the availability of data from adoption studies, and partly from the fact that both of these produced findings that were in good agreement with the results of family studies.

The third era, extending roughly from the 1980s to the early 1990s, was mainly characterised by denial of the importance of environmental influences. Three major challenges led to this shift in view. First, in parallel with Thomas, Chess, and Birch's (1968) findings on the importance of children's temperamental characteristics, there was an important and influential paper by Bell (1968) in which he pointed out that many of the statistical associations purported to reflect socialisation influences might reflect the impact of children on family functioning as much

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as the impact of patterns of upbringing on child behaviour. The second challenge came from behavioural genetics through Plomin and Daniels' (1987) argument that the weight of evidence suggested that, for most (but not all) forms of psychopathology, environmental influences tended to make children in the same family different rather than similar. This was used, or rather misused, by many commentators, to conclude that family-wide influences (such as discord/conflict or poverty or social disadvantage) were unimportant (Harris 1998; Rowe, 1994; Scarr, 1992). This was always a mistaken inference. What the findings actually meant was that family-wide influences tended to impinge to a different degree and in different ways on children in the same family (Plomin, 1994). That was a very important observation but it definitely did not mean that family-wide influences were irrelevant. A further challenge also came from behavioural genetics (Plomin & Bergeman, 1991), in relation to the evidence that the crucial role of gene–environment correlations meant that some of the associations between environmental risk factors and mental disorder were actually genetically, rather than environmentally, mediated. That was an important challenge that had to be taken seriously. Nevertheless, the evidence did not show that environmental mediation was unimportant. Rather, it showed that statistical associations between environmental risk factors and psychopathology might be, in part, genetically mediated. Overall rejection of the importance of environmental influences was always unwarranted.

This same period (in other words, the 1980s to early 1990s) was also characterised by the development of the application of molecular genetic strategies to psychiatric genetics. At first, this was in terms of the hope and expectation that the aetiology of many psychiatric disorders would be found to derive from the effects of individual mutated genes that had a relatively direct causal role on mental disorder (Kidd, 1991). In many ways, this was a dispiriting period because many of the initial claims of finding a gene 'for' some mental disorder were not replicated and subsequently had to be withdrawn (Rutter, 1994). This was a period of disillusionment, disenchantment and pessimism about the possibility of truly understanding the role of specific identified genes in the causation of psychopathology.

The fourth era, which may be perhaps seen as extending from the early 1990s to the present time, has involved five major changes in concept. First, there has been an abandonment of the notion of single basic causes and an acceptance of the multifactorial origin of most disorders. This shift in concept was not at all specific to mental disorders; rather, it has covered more or less the whole of medicine (Rutter, 2003, 2005, in press a). There are two key components in the current view. There is the acceptance that almost all risk factors, whether genetic or environmental, involve probabilistic, rather than deterministic, effects. In addition, there has come a recognition that risk effects extend throughout the normal distribution and not just at the extreme end. Thus, this has been shown with respect to cholesterol levels and the risk of heart attacks just as it has also been shown with respect to the risks of smoking on lung cancer.

A second feature of this same time period has been the growth in the criticisms of behavioural genetics (James, 2003; Joseph, 2003; Rose, 1995, 1998; see also Rose, Lewontin, & Kamin, 1984). In part, the criticisms have focused on the real and imagined deficiencies in the empirical behavioural genetics studies but, in part, they have focused on the supposed dangers of an extreme biological, or genetic, determinism. As reviewed by Rutter (in press a), there is some substance to the criticisms that have been put forward but, equally, it is clear that they do not undermine in any serious way the overall conclusion that genetic influences play a major role in individual differences in the liability to a broad range of mental disorders.

The third feature of this era has been the realisation that there are many research strategies that can provide an effective test of environmental mediation (Rutter, Pickles, Murray, & Eaves, 2001; Rutter, 2005). Twin and adoption strategies provide one means of doing this, but so do natural experiments of various kinds. The conclusion from studies that provide a proper rigorous test of environmental mediation (through taking account of key alternatives such as genetic mediation, social selection and person effects on the environment) is that there are valid environmentally mediated risk effects on psychological functioning and on mental disorders and, moreover, that these include variations within the normal range of environments, as well as at the extreme (Rutter, 2005). In short, there was a re-establishment of the reality of the importance of environmental influences on psychopathology.

A fourth feature of the era between the 1990s and the present time has been the re-emergence of an interest in gene–environment interplay (Moffitt, Caspi, & Rutter, 2005, in press). This has a long history in genetics as exemplified by Haldane's paper in 1946 and by two key papers in the 1970s (Eaves, Last, Martin, & Jinks, 1977; Plomin, DeFries, & Loehlin, 1977). New concepts and new findings, however, have meant that there has had to be a greater acceptance of the importance of gene–environment interplay (Rutter & Silberg, 2002). These considerations are discussed more fully below.

A fifth feature of this time period has been the recognition of the importance of epigenetic mechanisms (Jaenisch & Bird, 2003). In early years there had been the complete dismissal of the possibility that environments could have an effect on genetic mechanisms and it was really important that research showed that this dismissal was quite

misguided. The key consideration was the recognition that genetic effects were crucially dependent on gene expression and that such expression was influenced by a wide range of factors, including environmental features. These findings are considered more fully below, but the evidence played a major role in forcing people to recognise that the straightforward deterministic view of genetic effects was mistaken.

Gene–environment interplay is a rather general term that covers several rather divergent concepts with different meanings and different implications. In this review, we evaluate the research evidence on four varieties of gene–environment interplay. First, we consider epigenetic mechanisms by which environmental influences alter the effects of genes. Second, we focus on variations in heritability according to environmental circumstances. Third, we discuss what is known on gene–environment correlations. Finally, we assess concepts and findings on the interaction between specific identified genes and specific measured environmental risk factors. Rutter et al. (1990a, 1990b, 1999a, 1999b) provided reviews of methods and findings of earlier research; here we mainly focus on research in the past six years. However, in order to provide an understanding of what may be involved in gene–environment interplay, we need to start with a simplified account of some of the key features of how genes 'work'.

Genetic mechanisms

Popular science writers and, unfortunately, some scientists often make reference to genes 'for' schizophrenia, intelligence or depression. Of course, geneticists are well aware that genes are not 'for' any of those traits (Kendler, 2005b). It might be thought that this terminology is simply a convenient shorthand means of expressing the finding that genes play some contributory role in influencing individual variations in the liability for these traits. Nevertheless, the terminology is misleading in a more serious way than that. To begin with, apart from the exception of the rare circumstances in which there are Mendelian effects in which a single gene major pathogenic mutation causes somatic malfunction that involves mental disorder, the genetic effects on the liability to psychiatric disorders are both much weaker and much more indirect than the 'genes for' terminology conveys. However, even beyond that, the terminology is misleading because of the wrong impression conveyed of how genes operate.

The conventional view has been that DNA (which carries the inherited genetic information) specifies the synthesis of polypeptides, which ultimately go on to form proteins, and that it is these proteins that are the 'workhorses' that bring about the phenotypic effects. That is not wholly wrong but it is a misleading oversimplification (Lewin, 2004; Strachan & Reid, 2004; Rutter, in press a). The DNA (meaning the sequence of the four bases that make up the triplets of 'codons' that provide the genetic information) constitutes the first phase of the process. However, the DNA, as such, has no effect on proteins. Rather, it specifies the synthesis of messenger RNA and it is then the messenger RNA that specifies the synthesis of polypeptides, which ultimately go on to form proteins. The importance of recognising this multi-phase causal process is that the process (called transcription) by which the DNA directs the synthesis of messenger RNA molecules is influenced by a range of other factors, both genetic and environmental. The genetic influences comprise transcription factors that collectively are known as the 'promoter'. Some of these are distant from the genes that they are influencing and they are called trans-acting because they have to migrate to the site where they act. In addition, there are other factors that are said to be *cis*-acting because their function is local and limited to the DNA duplex on which they reside. In addition, there are enhancers that increase the transcription activity in specific genes and silencers that inhibit them. Although, by convention, these various transcriptional factors are not usually termed genes, they are made up of DNA sequences and will be inherited along with the rest of the DNA.

The second step in the causal chain involves what is called 'translation', meaning the process by which the messenger RNA specifies the production of polypeptides. Unlike transcription, which takes place in the nucleus of cells, translation takes place in the ribosomes in the large RNA-protein complexes outside the nucleus in the surrounding cytoplasm. The conversion of polypeptides to proteins involves the folding of proteins, which is crucial for their effects. The precise mechanisms involved in this folding process are unclear. To a major extent, they are driven by genes, but also they are influenced by the environment of the cell and, especially, by the confining cell membranes. Beyond that, the effects of these proteins are also influenced by the interplay among different protein products, such interplay being ill-understood at the moment.

The complexities do not end there. The DNA content of all cells in the same organism is much the same. What makes the various cell types different (meaning whether they are liver cells or brain cells or blood cells) is that only a proportion of the genes in any one cell are significantly 'expressed' (meaning that they are functionally activated) and that the pattern of expressed genes varies among different cell types. Accordingly there have to be features that control this selective activation of specific genes in different tissues; these features are both genetic and environmental.

Basically this selective activation involves the transcriptional and translational elements already noted, plus epigenetic mechanisms particularly involving methylation. Some genes, known as housekeeping genes, need to be expressed in all cells

because they deal with general functions such as protein synthesis. On the other hand, many genes are expressed only in particular body tissues, or only during a particular developmental phase. It is important that some genes can have different functions in different tissues as a result of tissue-specific promoters or tissue-specific alternative splicing (see below). The implication is that the differential patterns of gene expression provide one way by which a single gene can have multiple effects. A key feature of gene expression is that it can be altered in a reversible way by extra-cellular signals and by environmental influences. Although DNA starts off the causal chain, what really matters is the expression of the genes (in terms of messenger RNA). There are no genetic effects without this expression. Unlike the operation of DNA, which is active in all cells, gene expression tends to be specific to particular body tissues and to particular phases of development. This class of mechanisms has been called epigenesis. The effects are distinctive in that they involve heritable states that do not depend on the DNA sequence. In other words, they do not alter the DNA sequence that constitutes the genetic code that is relevant for a particular trait. That is why they are called epigenetic rather than genetic. Some of the key features of the process involved are discussed further below.

Several different features of the processes of transcription and translation are relevant to understanding how genes work. First, the classical notion of genes focused on those involved in coding for proteins. That makes sense because the effects of genes are entirely through the proteins to which they lead. However, what is now abundantly clear is that only a tiny proportion of the inherited DNA gives rise to the messenger RNA that codes the specific proteins. At first it was thought that the rest of the DNA was just 'junk' that had no useful purpose, but it now seems that that is probably a misunderstanding. To begin with, much of the DNA that does not code for proteins is actually expressed, albeit with respect to non-protein-coding RNA transcripts (and, therefore, termed RNA genes). The crucial consideration is that the non-coding genes have a crucially important role in the transcriptional process. Thus, for example, it is known that one plays a key role in X chromosome inactivation (the mechanism that ensures that only one X chromosome in females is active and that the other is, in effect, switched off). For many years, it was assumed that (apart from the pseudoautosomal genes on the X and Y chromosomes that show equivalent dosage) X inactivation was general. It is now evident that some 15% of X-linked genes escape inactivation to some degree (Carrel & Willard, 2005). This means that some X-linked genes are expressed at higher levels in females than males. Also females, unlike males, are mosaics of two cell populations with respect to X-linked gene expression. It can be expected that these will have clinical implications, but it is not yet known what these are. Non-coding RNA genes also play a role in genomic imprinting (the mechanism by which the effects of mutant genes are influenced by whether or not they are transmitted by the mother or the father). This is relevant, for example, in the case of Prader-Willi syndrome and Angelman's syndrome (Skuse & Kuntsi, 2002).

Several considerations flow from what is known about these transcription and translation processes. First, this knowledge necessarily affects the way that one thinks about what is a gene. The original concept of a gene was an inherited element that, through the messenger RNA, coded for a particular protein. It is now clear that, with respect to any single protein, only one gene may code for its production, but multiple inherited DNA elements influence its transcription and expression. That means, amongst other things, that the genes that are responsible for contributing to the susceptibility to mental disorders may involve these non-protein-coding genes (such as promoters) rather than the traditional protein-coding genes (for examples see Rutter, in press a).

A second key consequence of the transcription process concerns the details of what is involved in steps leading from the DNA to the messenger RNA (mRNA). The DNA is made up of alternating 'exons' and 'introns'. Exons are the sequences represented in the mature RNA, which is what codes for the polypeptides that make up the proteins that bring about the real biological 'action'. Introns are the intervening sequence that do not code for proteins and which are removed during the process of transcription to produce DNA. The key point here is that this process, called splicing, occurs in such a way that a single gene may give rise to different exon combinations during RNA processing. That is, through alternative patterns of splicing, one gene may produce several types of mRNA (see Ast, 2005). This means that alternative splicing constitutes a further way (beyond variations in gene expression) in which the same gene may give rise to multiple different proteins with different effects. This provides a mechanism by which a single gene can have varied consequences (the so-called 'pleiotropic' effects of genes).

The selective activation of specific genes in different tissues, in other words the processes that underlie gene expression, are open to the mechanisms of epigenesis. DNA methylation and histone acetylation (two linked chemical processes) are involved in epigenetic mechanisms and these provide a way in which environmental influences can affect gene expression. They do not alter the gene sequence (and hence do not alter the genes themselves) but, because they do alter gene expression, they have a big effect on the consequences of genes. These are considered in more detail in the section below dealing with the effects of environments on genes. Putting these features together, a succinct way of expressing things is to say that, rather than there

being direct effects of a single gene on a single outcome, it is more appropriate to think of a dynamic process in which the effects of a single gene are influenced by multiple inherited DNA elements and by the actions of environments.

The third key feature concerns the nature of the genes that are relevant for psychopathology. In the early years of application of molecular genetics to psychiatry, the focus was on trying to find abnormal mutant genes that interfered with some vital function and, thereby, caused mental disease. The expectation, as it were, was that at least the serious disorders such as schizophrenia or bipolar disorder or autism would prove to be due to operation of several abnormal genes of this kind that brought about directly genetic effects that required no environmental influence. For a variety of reasons that possibility never seemed very likely (Rutter, 1994) but it was the dominant view for quite a few years (Kidd, 1991). It is now clear that single mutant genes account for only a very tiny minority of psychiatric disorders (such as Rett syndrome or early onset autosomal dominant Alzheimer disease). Much more often, the genes that have been found to provide susceptibility to mental disorders are normal allelic variations. Of course, in a real sense, all variations are mutations that have arisen in the course of evolution. Nevertheless, the distinction is an important one. The susceptibility genes that have been found differ from the pathogenic abnormal mutations in two ways; they are very common and they do not prevent vital functions. These genes that have been found to be involved in susceptibility to mental disorders have several important features. First, the allelic variations that carry risk are mostly very common, affecting, say, a third of the population even though the disorders for which they provide susceptibility are much rarer than that. Second, the allelic variations that carry risk do so at only a quite low probability level. Thus, as Kendler (2005b) has noted, the odds ratios are usually substantially less than two. Accordingly, it makes no sense to describe these as genes 'for' any particular mental disorder. They are implicated in the causal processes leading to the mental disorder, but only along with other genes and with a range of environmental influences. In short, they constitute part of multifactorial causation and not any direct genetic effect. Third, in most cases, the susceptibilities are dimensional, rather than categorical. That is to say, the risks need to be viewed as operating on a continuum rather than on a present/absent basis. It should be emphasised, incidentally, that this applies to the genes involved in multifactorial somatic disorders such as coronary artery disease, hypertension, asthma and diabetes just as much as psychiatric disorder. It is a general phenomenon, not one that is in any way specific to psychopathology.

The fourth point is that, in many instances, the genes seem to operate indirectly in the sense that they predispose to disorder only through their effects on exposure to risk environments or sensitivity to risk environments, rather than through a risk mechanism that might be viewed in any sense as directly leading to psychopathology. The evidence on these gene–environment correlations and interactions constitutes the bulk of this paper. However, at this point, the example of Alzheimer's disease may be used to illustrate how and why this may be important. The APO-E-4 allelic variation has been shown in numerous studies to carry a much-increased risk for Alzheimer's disease of the more usual late-onset variety (Farrer et al., 1997). As such, it is tempting to view it as a gene for this mental disorder. However, it is neither a necessary nor a sufficient cause. That is to say, there are many people with the APO-E-4 allelic variation who do not develop Alzheimer's disease and there are many people without this allelic variation who do. But that is not all. Not only does the APO-E-4 allelic variation carry susceptibility to Alzheimer's disease but also it carries susceptibility to the adverse consequences of responses to head injury and cerebral vascular disease (Saunders, 2000). Third, the risk for Alzheimer's disease associated with the APO-E 4 varies markedly by ethnicity (Farrer et al., 1997). Fourth, a study of transgenic mice has shown that 'environmental enrichment' results in a pronounced reduction in amyloid deposits as compared with mice raised in 'standard housing' conditions (Lazarov et al., 2005). It seems that the benefits may derive in part from increased expression of protective genes. Another mouse study, however, gave rise to different findings. Also, the prospective Nuns study (Mortimer, Snowdon, & Markesbery, 2003) in humans indicated that the benefits of early superior scholastic performance provided a reduced risk of dementia rather than an effect on the neuropathology as such. It may be concluded that it is likely that environmental factors may influence the course of Alzheimer's disease, although the mechanisms involved remain unclear. Fifth, although from a clinical perspective a sharp distinction is drawn between the normal processes of the decline in short-term memory with increasing age, and the pathological condition of Alzheimer's disease, the evidence suggests that the APO-E-4 allelic variation is involved in susceptibility to both (Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Small et al., 2000). Of course, we do not know that the same features will apply to other mental disorders but it is reasonable to suppose that they might well do so. Inevitably, all of this changes the way in which one needs to view the concept of susceptibility genes. In other words, they are vitally important in the causal processes that lead to mental disorder, but they may well not constitute necessary or sufficient causes of psychopathology. With that as a background, we need to turn to the evidence on four different forms of gene–environment interplay as they apply to psychopathology.

Effects of environments on genes[1]

The interest in epigenetic effects has come from two rather different sources. First, there has been an interest for a long time in the possible reasons for the discordance in monozygotic twin pairs with respect to disorders that have a very strong genetic influence – such as schizophrenia. Of course, this could arise through differences in their experiences but, also, it could derive from chance effects (see Wong, Gottesman, & Petronis, 2005). Thus, Petronis et al. (2003) compared the DNA methylation patterns in the blood cells of one pair of twins concordant with schizophrenia and one pair who were discordant, focusing on the promoter region of the dopamine D2 receptor gene. This was the focus because this was concerned with neurotransmitter functions thought to be important in schizophrenia. The results showed that the epigenetic patterns were more different in the discordant twin pair than in the concordant pair. Because the analysis concerned peripheral blood cells, it is likely that the differences in methylation arose from chance effects rather than from systematic environmental influences, but the latter are likely to be important in other circumstances. Not too much should be read into this single case study but the finding does emphasise the possible importance of differences in gene expression in accounting for differences in outcome among individuals with the same susceptibility genes and it points to the possible utility of using discordant MZ pairs in order to investigate epigenetic effects (Kato, Iwamoto, Kakiuchi, Kuratomi, & Okazaki, 2005). It has been suggested that chance epigenetic events might account for a substantial portion of phenotypic variance in relation to the development of schizophrenia (Petronis, 2004).

Second, there is a much more substantial body of research that has examined epigenetic effects in relation to the influences of specific environments. A particularly striking, albeit very unusual, example of epigenetic effects derived from a study of the effects of maternal diet on the coat colour of the offspring of a particular species of mouse (Waterland & Jirtle, 2003). The findings showed that, in keeping with a broader body of research into the chemical basis of epigenesis (Jaenisch & Bird 2003), the mechanism lay in methylation, which altered gene expression. The first step in the research was to establish that the hair colour was indeed associated with variations in the methylation of a promoter on a particular gene. The second step examined the effects of dietary methyl supplementation in order to test the causal inference. It was found that methyl supplementation was associated with hair colour changes and that this was a function of the increased methylation at a particular gene locus. A quite different environmental stimulus was studied by Cancedda et al. (2004). They found that raising mice in an experientially enriched environment accelerated the development of the visual system and that this was associated with altered gene expression leading to an increase in BDNF protein in the visual cortex of the brain.

These studies provided impressive demonstration of the potential importance of environmentally induced epigenetic effects but, at first sight, they seem far removed from influences on psychopathology. Because gene expression is tissue specific it is not usually feasible to study epigenetic effects on brain tissue in humans during life. Moreover, it is quite difficult in humans to provide the experimental control that is needed to separate prenatal, postnatal and genetic effects. The pioneering rat studies of Michael Meaney and his colleagues (Champagne et al., 2004; Cameron et al., 2005; Weaver et al., 2004) illustrate well the research strategy as applied to animals, and have done so with respect to aspects of nurturant experiences that seem closer to what might be important in humans. The starting point for their research was the observation that lactating mother rats varied markedly in the degree to which they licked and groomed their offspring and showed archback nursing, and that the individual differences were stable over the first week of lactation. Crucially, and interestingly, these differences in nurture and behaviour were not associated with overall differences in the time that the mothers spent with the pups. That is, what was being studied was the consequences for the offspring of a particular type of nurture on behaviour, and not just a difference in contact. These individual differences in maternal nurturing behaviour were associated with variations in the neurotransmitter dopamine in a particular part of the brain. Strikingly, it was observed that the variations in maternal behaviour were associated with individual differences in the offspring's behaviour and in the offspring's neuroendocrine response to stress.

The first research need following these initial observations was to determine whether the behavioural and endocrine differences in the offspring were genetic in origin. That is to say, were they a consequence of the DNA inherited from the rat parents or were they a consequence of the different patterns of rearing? The question was tackled by a cross-fostering research design in which the offspring of mothers with high licking and grooming behaviour were reared by mothers with low licking and grooming behaviour, and vice versa. The key question, then, was whether the endocrine responses in the behaviour of the offspring were a function of their biological parentage or their social rearing. The results clearly showed that the effects were a consequence of the rearing environment and not their biological inheritance.

[1] Parts of this section of the paper are based on the account in Rutter, in press a.

The next challenge in research by Michael Meaney and colleagues was to determine how rearing had altered the organism of the offspring so that behavioural consequences were transmitted to the next generation and persisted into adult life. What the research showed was that the maternal behaviour had lastingly altered the endocrine response to stress through tissue-specific effects on gene expression. In particular, the effects were on a specific gluco-corticoid receptor gene promoter in the hippocampus. It is noteworthy that, in this instance, the effects were not on a protein-producing gene but rather on a promoter gene that affected protein production indirectly through its effects on another gene. It was shown that the effects were specific to a particular part of the brain. The consequences of the effect on the promoter gene seemed to be carried through by the knock-on effects on serotonin activity. The investigators hypothesised that maternal care was altering the DNA methylation of this particular promoter gene and that this change was maintained into adulthood and, because of persistence, it was associated with differences in endocrine responses even in maturity. Their experimental work demonstrated that this hypothesis was indeed correct. Interestingly, however, the results showed that the group difference in DNA methylation occurred as a function of maternal behaviour only during the first week of life. What happened later did not appear to have the same consequence.

In order to test the causal inference more thoroughly, the next question was whether this rearing-mediated epigenetic marking was actually irreversible or whether there were ways in which it could be changed in later life. The findings showed that treatment with a drug called trichostatin-A (TSA) did go some way to reversing the maternal effect of methylation. The detailed findings showed that it did this through an effect on acetylation, which is a kind of balancing chemical process that counteracts methylation. The next question was whether this reversal of the early DNA methylation actually made any difference to the endocrine response to stress. The findings showed that it did, providing a convincing demonstration that the methylation effect truly caused the behavioural difference. The most recent research from this group has shown that these intergenerational effects of early patterns of nurturing also affect the sexual responsiveness of the offspring (Cameron et al., 2005).

The precise sequence of elements in the epigenetic mechanisms involved in the intergenerational transmission of the effects of early maternal nurturing have not been fully tested by other investigators but key elements have been confirmed in other well-controlled studies. Thus, a parallel study by a different research group contrasted prenatal and postnatal effects (Francis, Insel, Szegda, Campbell, & Martin, 2003). A single in-bred mouse strain was cross-fostered prenatally by removing cells after mating for implantation in foster mice. Postnatal fostering was performed soon after birth by transferring newborn pups from these litters to two genetically different parturient females. The findings showed that the prenatal and postnatal environment influences combined to produce marked differences in behaviour thought to reflect emotionality. Because the groups being compared were genetically identical, the effects had to be environmentally mediated. Because of the combined effect of the prenatal and postnatal environment, the findings suggested that the prenatal environment may prime the developing organism to respond in a particular way to postnatal care.

Fleming's research group (Fleming et al., 2002) used the research stratagem of separating mother rats and their offspring during the nesting period. The offspring were then followed through to adulthood, mated and tested with their own offspring. It was found that maternal behaviour deficits in the first generation offspring were systematically related to the degree of early maternal deprivation. Similar, but weaker, effects were found for the second generation offspring. Interestingly, very brief separations (fifteen minutes) led to an increase in maternal nurturant behaviour on reunion. In order to determine if the effects of more extended separations (twenty-four hours) could be remodelled by experimental stimulations, Gonzalez, Lovic, Ward, Wainwright, and Fleming (2001) reared pups artificially and then determined the effects of more or less stimulation during the pre-weaning period. Partial reversal of deprivation effects was found. In order to examine the biological mediation of these intergenerational environmental effects of mothering, Fleming et al. (2002) examined fos-like immunoreactivity in the medial preoptic area of rats sacrificed when juvenile. Reduced levels of c-fos expression were found, an effect shown to persist into adulthood, together with the behavioural effects of reduced nurturing. It may be concluded that the broad pattern of findings from Meaney et al.'s research has been confirmed.

The findings on environmentally induced epigenetic effects are compelling in being based on a series of particularly rigorous, creative and well-controlled experiments but it is necessary to go on to consider whether, and how, the findings might have broader implications for human functioning, with particular respect to influences on psychopathology. It would be a mistake to speculate on the human equivalent of the licking and grooming behaviour of these rat mothers and it would be inappropriate to view this as something that would generally apply to nurturing care. That is because the findings in rats applied only to nurturing in the first week of life.

On the other hand, what probably are generalisable are the mechanisms involved in the effects of psychosocial experience on DNA methylation, and consequences of such methylation effects on biological functioning and on behaviour. The human feature to which extrapolation of these epigenetic

effects is most likely to apply concerns the area of so-called developmental programming (Barker, Eriksson, Forsen, & Osmond, 2002; Bateson et al., 2004; Rutter et al., 2004; Rutter, in press a). This is a term that has been applied to the effects of experiences on brain development (or the development of other organs) either because certain basic experiences are essential for there to be normal development during a sensitive period in which brain structures are laid down, or because the particular experiences during such sensitive periods serve to adapt the organism to the environmental conditions prevailing at that time. As emphasised by Meaney and his colleagues (Cameron et al., 2005), the environmental effects with respect to experience-adaptive programming apply to normal variations within the environment and not just to pathological extremes of abnormal environments. Moreover, the consequences cannot sensibly be viewed as either good or bad in absolute terms. That is to say, the implication is that the consequences are adaptive with respect to particular environmental circumstances. Although we are only just at the beginning of achieving any kind of understanding of the implications of environmentally induced epigenetic effects, already the results show that the clean separation of nature and nature, or of genes and environment as more broadly conceptualised, is misleading. Environments cannot influence gene sequences but they can and do influence gene expression.

One human example regarding gene expression that is relevant to possible major effects in later life concerns tobacco smoking. The requirement that gene expression must be studied in relevant tissues was met through the use of bronchoscopy to obtain airways cells by brushings from the airway linings. The epidemiological background of the effects of smoking concerned the strong and consistent evidence that smoking is implicated in the causation of lung cancer but that there is considerable individual variation in response (only some ten to twenty percent of smokers actually develop lung cancer) and that the risks of lung cancer persist a surprisingly long time after stopping smoking (Doll, Peto, Boreham, & Sutherland, 2004). An interesting study by Spira et al. (2004) compared gene expression in smokers and non-smokers, finding that cigarette smoking affected the expression of multiple genes involved with carcinogenesis and the regulation of airway inflammation. The expression level of these genes among former smokers began to resemble those of non-smokers about two years after people stopped smoking. Nevertheless, there were a few genes that failed to revert to non-smoker levels even after many years of not smoking.

An additional method of studying gene expression in human tissues involves the study of post-mortem specimens. Mirnics, Middleton, Stanwood, Lewis, and Levitt (2001) compared gene expression profiles from ten schizophrenia-control pairs, finding reduced expression of RGS4, a regulator of g-protein signalling. As concluded by Harrison and Weinberger (2005), the findings so far are only suggestive for this possible schizophrenia susceptibility gene. Veldic, Guidotti, Maloku, David, and Costa (2005) compared brain slices from 19 patients with schizophrenia, 19 with bipolar disorder and 26 individuals without psychiatric disorder. The findings showed an overexpression of cortical DNA – methyltransferase in both the psychiatric groups (as compared with controls), a difference that could not be accounted for by the use of typical or atypical psychotropic medication (apart from the use of valproate). The findings are consistent with the view that the causal mechanism may be related to epigenetic hypermethylation of gene promoters involved with reelin. Replication is still needed, and the results on their own do not prove causation, but the findings do point to the possibility of epigenetic, as well as genetic, effects in the causal pathways leading to schizophrenia (Petronis, 2004).

The field of epigenetics, and of gene expression, is much too new for any firm conclusions, but already it is well demonstrated that it is possible for environmental effects to influence gene expression. As such, the effects are relevant to the crucial question of what experiences do to the organism in order for there to be persistent sequelae. It is too early to know whether these environmental effects on gene expression will be relevant to nature–nurture interplay in the causation of psychopathology but it has been suggested that this is likely to prove to be the case (Abdolmaleky et al., 2004).

Before leaving the topic of epigenetics, it is necessary to consider the broader topic of what experiences do to the organism in order for there to be prolonged sequelae of one kind or another. The examples of epigenetic effects discussed here all concern physiological or biochemical pathways likely to be genetically influenced to a major degree. Thus, this would apply, for example, to hormonal effects in relation to stress, carcinogenic effects, dietary effects and effects on biological programming. In all probability, epigenetic mechanisms are also quite likely to be implicated in prenatal effects of many kinds (Coe & Lubach, 2005). In addition, it is probable that they play a role in the gene–environment interactions discussed below, because the interaction findings imply that the environmental effects operate on the same neurotransmitters that are influenced by genes. What then are the environmental effects that are less likely to be mediated by epigenetic mechanisms? Probably, two main varieties stand out among the range of processes that have to be considered (Rutter, 1989a). First, there are the environmental effects that rely on how people think about their experiences. Thus, there is much evidence that jobs that involve a lack of control carry with them a substantially increased risk of physical ill-health (Marmot, 2004). Obviously, the thoughts about lack of control have to have a neural basis, and also it is highly likely that

people's tendency to think in particular ways will be genetically influenced. On the other hand, it is not self-evident that neurochemical processes will account for the *particular* thought patterns. The same probably applies to the effects of relative deprivation because the evidence suggests that the risks stem from being worse off than other people rather than from absolute levels of poverty (Marmot & Wilkinson, 1999; Wilkinson & Marmot, 2003).

Second, probably, much the same applies to the mechanisms involved in interactions with other people (see section below on gene–environment correlations). Again, genes play an important contributory role in these effects but the mechanisms are basically interpersonal rather than genetic. Possibly, the same applies to the effects of living in socially disorganised areas (Brooks-Gunn, Duncan, & Aber, 1997; Caspi, Taylor, Moffitt, & Plomin, 2000; Sampson, Raudenbush, & Earls, 1997). The findings suggest that the risks derive from a lack of social support and community cohesion. Once more, such effects will affect genetically influenced systems of various kinds but it is less likely that risk or protective effects will be mediated by epigenetic effects on gene expression.

It is obvious that all these suggestions are speculative. There are, we suggest, two firm conclusions. First, experiences *do* affect gene expression, and it must be anticipated that these mechanisms will prove to be important in a much wider range of environmental effects than those investigated so far. Second, epigenetic effects do not constitute the only possible process by which psychosocial (or physical) experiences bring about enduring psychological consequences and indeed it is unknown how relevant epigenetic effects will prove to be for psychopathology. The overriding need is for research that is designed to pit one mediating mechanism against alternative possibilities with respect to specific experiences and particular outcomes. Up to now, such investigations have not been recognised as needing to be a research priority. We suggest that they need to be moved up the research agenda. As Kendler (2005a) has emphasised, psychopathological mechanisms need to be considered in relation to whole organism physiology and psychology, and not just at the cellular level.

Variations in genetic influence according to environmental circumstances

From the outset, geneticists have emphasised that heritability is a statistic that applies to population variance and not to individuals or to traits as a fixed feature. A high heritability means that genetic factors account for much of the variation in the liability to show a particular trait in a particular population at a particular point in time. It does not mean that genetic factors play a major role in the causation of that trait in any one individual. Equally, it does not mean that genetic factors account for that particular proportion of the population variance for that trait in all circumstances. If genetic conditions change, or if environmental circumstances alter, the heritability will not remain the same.

Stoolmiller (1999) has emphasised the effect on heritability estimates of restrictions in environmental range in adoption studies, and exactly the same will apply to twin studies. The main methodological message is that heritability estimates are unlikely to be comparable if the samples studied differ markedly in level, or range, of environmental risk. In addition, however, heritability estimates will be influenced by the operation of gene–environment interactions ($G \times E$), as well as by other models of variations in the manner of interplay between genes and environments.

Shanahan and Hofer (2005) have suggested the need to consider four main models. First, as postulated by a stress-diathesis concept, and by gene–environment interactions ($G \times E$), there may be environmental triggering of a genetic susceptibility that mainly operates by virtue of an effect on responsivity to risk features of the environment. Secondly, the social context may compensate for a genetic diathesis. Usually, this will constitute no more than the opposite end of the continuum operating in the stress-diathesis model but it could work by a different mechanism. Third, there may be environmental constraints that, by limiting choices or opportunities, reduce the role of genetic influences as they affect individual differences in traits likely to be affected by choices or opportunities. Fourth, environmental contexts may serve to accentuate or enhance the effect of genetic influences. Thus, Bronfenbrenner and Ceci (1994) put forward a bioecological model that postulated that advantageous proximal environments (meaning those that directly impinged on the individual) would increase the actualisation of genetic influences.

Clearly it would be informative to test these alternative models. Although, for many mental disorders, the heritability has remained reasonably consistent across a range of populations (thus the heritability of schizophrenia, autism, bipolar disorder and attention deficit/hyperactivity disorder has been consistently above the 50% mark), that has not applied to all traits. Accordingly, there have been various studies seeking to use variations in heritability, or in genetic influences as measured in other ways, to investigate the mechanisms involved in gene–environment interplay. The studies fall into four main groups.

Effects on heritability of a major environmental hazard

First, there are studies testing the effects on heritability of the occurrence of a major environmental hazard known to have substantial psychopathological effects. The advantages of these studies are

both that the focus is on a known environmentally mediated risk effect and that there is a specific directional hypothesis – namely that heritability will be less in the presence of the major environmental hazard. Koeppen-Schomerus, Eley, Wolke, Gringras, and Plomin (2000) adopted this strategy with respect to their examination of the heritability of cognitive functioning in relation to the presence of very premature birth (below 32 weeks of gestation) and the associated obstetric and perinatal complications. Extreme prematurity (affecting 5% of the sample) was found to be associated with a large decrement in nonverbal intelligence (a finding in keeping with the results of other research – Marlow, 2004; Marlow, Wolke, Bracewell, & Samara, 2005). The twin analysis showed that this effect was entirely environmentally mediated. This contrasted with the finding in the main sample (with a gestational age of at least 34 weeks, in which genetic factors accounted for about a quarter of the population variance in nonverbal cognitive performance). The implication was that when there was the presence of an environmental risk factor that had a major deleterious impact on cognitive functioning, the role of genetic influences was proportionately less. It should be noted, however, that the statistical power was low and the difference fell short of statistical significance (although it was significant for verbal skills). Asbury, Wachs, and Plomin (in press) found a similar effect on verbal scores at age 4 years for the 15% at greatest medical risk (indexed by low birth weight, time spent in special care etc.), the heritability being 11% as compared with 70% in the top 15%, and 44% in the sample as a whole. The difference, however, fell short of statistical significance.

Wichers et al. (2002) undertook a similar analysis in the East Flanders Prospective Twin Study of 6- to 17-year-old twins, focusing on problem behaviour rather than cognitive level. The pattern of findings was closely similar; heritability was significantly lower in children with a birth weight that was very low in relation to gestational age than in those with a normal (or above average) birth weight. The implication is that a powerful environmental risk factor lowered the impact of genetic factors.

The findings of this group of studies are best conceptualised as representing a demonstration of the basic feature of heritability; namely, that the population variance attributable to genetic factors may be expected to be lower in any subsection of the population exposed to a major adverse environmental influence known to impact on the trait being investigated. The evidence, albeit based on a tiny number of studies, confirms that this does indeed happen.

Effects on heritability of dimensional variations in some environmentally defined risk factor

A second group of studies have used a broadly similar approach to examine the effects on heritability of dimensional variations in some environmentally defined risk factor. For the most part, these studies have been concerned with testing the bioecological model, which predicts a greater heritability in the presence of advantageous proximal environments. Four studies have applied the approach to measures of intelligence. Van den Oord and Rowe (1998) in a study of children, with an average age of 9 years, found no effect of the quality of the family environment on the heritability of reading and mathematics proficiency. The study had the merit of including both more proximal family measures (using the HOME scale) and more distal ones (such as family poverty or educational level of the parents). Both sets of family measures correlated about .3 to .4 with achievement.

The second study, by the same authors (Rowe, Jacobson, & van den Oord, 1999), found, by contrast, a marked moderating effect of parental education on the heritability of verbal intelligence in adolescents. Among highly educated families, the heritability was 74% compared with 26% in less well-educated families – in keeping with the expectation of the bioecological model.

The third study, by Turkheimer, Haley, Waldron, D'Onofrio, and Gottesman (2003), found the same major moderating effect of family circumstances, in their case indexed by socio-economic status, on IQ at age 7 years. It failed to replicate the Rowe et al. (1999) finding that the effect was on verbal IQ (although there was a trend in the same direction that fell well short of statistical significance), the environmental moderation applying significantly only to nonverbal IQ.

The fourth study by Asbury et al. (in press) similarly tested the bioecological model, in their case with a large sample (4,446) of 4-year-old twins, with findings that were almost entirely negative. The study examined a broad range of environmental variables, and did so systematically at a variety of points on the distribution, but the study is limited by the fact that the risk effects of the measured variables were only modest. None of the separate comparisons was statistically significant but the overall pattern was largely consistent in showing trends that were the reverse of those in the Rowe et al. (1999) and Turkheimer et al. (2003) studies. Thus, for example, the heritability was 81% in the bottom 15% of the SES distribution as compared with 49% in the top 15%. Similarly, the contrast for family chaos was between 72% in the most chaotic 15% versus 21% in the least chaotic. The authors concluded that, insofar as consistent trends could be used as a guide, the findings suggested that they were more compatible with a diathesis-stress model than a bioecological one.

One other study tackled the same question, in relation to antisocial behaviour rather than IQ (Button, Scourfield, Martin, Purcell, & McGuffin, 2005). It was found that the heritability of antisocial

behaviour was much greater in the absence of serious family dysfunction (which was found to have a major effect on such behaviour) than it was in the presence of such dysfunction – 0% in the most dysfunctional 10% and 80% in the least dysfunctional. The findings are limited, however, by the use of the same rater (a parent) for both the dysfunction and conduct problems, causing the possibility of a halo effect bias. The lack of longitudinal data also meant that the direction of the causal effect could not be determined. Most crucially, the authors erroneously concluded that the findings pointed to the genes operating through susceptibility to family dysfunction. If anything, the findings run counter to the hypothesis of G × E and therefore also differ from other research findings (see section below on G × E).

The Rowe et al. (1999) and Turkheimer et al. (2003) findings have aroused a great deal of interest among social scientists, if only because of their evidence that the heritability of IQ might be quite low in the presence of social disadvantage. Nevertheless, conclusions are necessarily severely constrained by three major considerations. First, the findings are contradictory. Neither van den Oord and Rowe (1998) nor Asbury et al. (in press) found the same effect and even the Rowe et al. (1999) and Turkheimer et al. (2003) findings contradict each other – in that the former found a moderating effect on verbal IQ whereas the latter found it only on nonverbal IQ. Of course, sample variations (such as in age or measures) might be important, but the point is that the evidence so far is inconsistent and contradictory. The bioecological model puts forward an intriguing possibility but the evidence in support to date is mixed. The second consideration is that with variables that apply to whole families (as is the case with SES and parental education), there is uncertainty over the extent to which the effect is genetically or environmentally mediated. As Turkheimer, D'Onofrio, Maes, and Eaves (in press) have pointed out, twin designs as ordinarily employed cannot quantify the genetic or environmental mediation of a risk variable that is measured only at a family, rather than child-specific, level. Thirdly, as Shanahan and Hofer (2005) emphasised, the bioecological model applies to proximal environmental influences that impinge on the individual, and the same might well not apply to broad distal influences such as SES.

We suggest that, if researchers are to test the bioecological model in an adequate fashion, it will be necessary to use child-specific measures that assess proximal influences, and to employ designs that can test for the environmental mediation of risk effects at different points on the distribution. If the risks mainly apply in extreme circumstances (as Scarr, 1992, claimed), then the model testing will need to take that into account as a possibility.

Societal moderators of heritability as implied by cohort effects or variations in some broad social variable

A third approach has been to examine possible societal moderators in terms of cohort effects or variations in some broad social variable (see Rutter & Silberg, 2002; Shanahan & Hofer, 2005). The question here is whether heritability changes over time when environmental circumstances alter in some major way or vary across segments of the population that differ in their constraints or opportunity for expression of individual differences.

Two general notions appear to have motivated these studies. First, it has been proposed that when there are widespread social constraints discouraging a behaviour, heritability will tend to be relatively low. By contrast, when constraints are removed or diminished, genetic effects become more influential (in other words, the third model put forward by Shanahan & Hofer, 2005). Many of the findings have been interpreted as in keeping with that hypothesis. For example, Heath, Jardine, and Martin (1989) found that the heritability of alcohol consumption was lower in married than in unmarried women, this being so in both younger and older age groups. Boomsma, de Geus, van Baal, and Koopmans (1999) found that a religious upbringing was associated with a lower heritability for 'disinhibition' (assessed in terms of drinking, going to parties, and having a variety of sexual partners). The interaction was significant in males; indeed, in those with a religious upbringing, genetic influences had no significant effect on individual differences in disinhibition. The trend in females was similar but not so strong. Koopmans, Slutske, van Baal, and Boomsma (1999) found the same with respect to alcohol use in females, although not in males.

Dunne et al. (1997) found that women and men born between 1922 and 1952, who would have reached adolescence during an era when social controls inhibiting sexual intercourse were relatively strong, showed a low heritability for the variance in the age of first intercourse (32% in women and 0% in men). By contrast, in those born between 1952 and 1965, so reaching adolescence in an era of greater sexual tolerance, the heritabilities were 49% and 72% respectively for women and men. Kendler, Thornton, and Pedersen (2000) found a rise over time in the heritability of smoking in women as smoking became more sociably acceptable, but no difference in men. Also, Dick and her colleagues (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001; Rose, Dick, Viken, & Kaprio, 2001), in a Finnish twin sample, found that the genetic influences on adolescent alcohol use were substantially greater in individuals living in urban areas with many young adults, and a pattern of high migration (assumed to index low social control). Specifically, they found a

heritability of 60% in areas with the highest migration, but only 16% in areas with the lowest migration. The implication is that low social control increases heritability.

The findings are impressive but two main concerns need to be raised. First, inconsistencies are apparent. Why, for example, are there sex differences, so that several studies have found effects in women but not in men, but Boomsma et al. (1999) found that the trends were stronger for males? Why did Heath et al. (1993) find no secular trend for smoking initiation, whereas Kendler et al. (2000) did find a trend? Second, none of the studies had measures of social control. There were reasons for thinking that it is likely that controls had changed over time, but there was a lack of evidence that that was actually the case. Third, the studies of social control have, very reasonably, focused on behaviours (such as smoking, drinking and early sexual intercourse) that are susceptible to social controls. If, however, the mediating variable truly is control, the findings should not apply to traits for which social control is less likely to be critical. Accordingly, why did Heath, Eaves, and Martin (1998) find that a married-like relationship reduced the heritability of depression in all age groups. Of course, marriage involves far more than social control. But if queries are raised on which aspects of marriage matter in relation to depression, should not the same queries be raised with regard to effects on other variables?

One of the very few studies (albeit not based on secular trends) to measure control was that undertaken by Johnson and Krueger (2005). Its focus was on perceived self-control over life circumstances, rather than the external societal controls implied by the drug use/sexual activity time trends studies. Also its focus was on physical ill-health rather than psychological functioning. In brief, the statistical modelling suggested that genetic variance increased, rather than decreased, with greater perceived control. They point out that the situation is different from that with high IQ because IQ is an adaptive trait, whereas physical ill-health is not. The paper also notes the complexity of studying gene–environment interplay when there are gene–environment correlations. The finding awaits replication, but the point of referring to it here is that it provides the only example we could find of an attempt to measure and model the hypothesised mediator.

The second general notion has been that heritability should increase if opportunities for the expression of a trait become greater. Thus, Heath, Kendler, Eaves, and Markell (1985) found an increase in the heritability of educational attainment in Norwegian males during a period in which educational opportunities became more widely available. No such effect was found in females. Silventoinen, Kaprio, Lahelma, and Koskenvuo (2000) found an increase in the heritability of height among Finnish men and women over a period of 30 years (a birth date before 1928 to a birth date of 1957). The rise was small – from 76% to 81% in men and from 66% to 82% in females – but significant. The change coincided with a time in which there was an overall increase in height of some 5 cm and both the rise in mean height and the increase in heritability were attributed to improved nutrition. The data are far too sparse for general conclusions but the findings are consistent with an increase in heritability with the provision of better opportunities. The overall implication from the cohort studies that heritability will vary according to whether the social context constrains expressions of individual proclivities, or frees such expression, is plausible, but the need is to have measures of such contextual effects.

Changes over time in identified gene effects

The fourth approach involves examining differences in the protective effects of an identified gene with a known action, according to social context. The ALDH2 gene, which leads to a severe flushing reaction after ingestion of alcohol, has been found to have an important protective effect against alcoholism in Asiatic people with the gene. Higuchi et al. (1994) reported that the increase (from 2.5% to 13%) of heterozygotes in alcoholics in Japan between 1979 and 1992 (a period in which there was a marked increase in alcohol consumption) pointed to a diminution of the protective genetic effect of the heterozygote as a consequence of a rise in the cultural acceptance of heavy drinking. In a small Israeli sample, Hasin et al. (2002) reported that the suppressive effect on alcohol consumption of the ADH2*2 genotype was less among Russian Jews who had been exposed to an environment of heavy drinking prior to immigration, than among Ashkenazi and Sephardic Jews who had not been exposed to such an environment. As with Higuchi et al. (1994), the inference is that low social controls were associated with a reduced heritability. The strategy of using identified genes is a good one but, once more, the need is to move from inferences on social control to measurement of such control.

Overview of variations in heritability findings

The findings on the variations in heritability according to differences in environmental circumstances have been important in confirming the genetic assumption that heritability levels are specific to particular populations. The levels are likely to go up or down whenever there are major changes in the balance between genetic or environmental effects on phenotypic variation. From the outset, behavioural geneticists have been at pains to emphasise that this is so, but the reminder is useful in countering the occasional tendency to misinterpret heritabilities as meaning that there is some absolute true level that is

invariant over time and over differing physical and social conditions. There is not, and cannot be, any fixed level of heritability.

The research into variations in heritability, however, has had the much more ambitious, and potentially valuable, goal of identifying the mechanisms that may be involved. As we have noted, there are real alternatives to be considered. Thus, if genetic effects operate through influences on sensitivity to the environment, the effect of an increase in environmental risks will be to increase heritability (as a result of the increased effect of the gene–environment interaction, G × E, on population variance in the trait affected by G × E). As we discuss in more detail in a later section, there is good evidence that this does happen.

Also, however, it has been argued that the power of environmental proximal processes to actualise genetic potentials will be greater in advantaged stable environments than in disadvantaged, disorganised ones (Bronfenbrenner & Ceci, 1994). This leads to an opposite prediction regarding the effects of greater environmental risk on heritability; namely, that it should fall rather than rise. Of course, it is entirely possible for both mechanisms to be operative in different circumstances. If research into variations in heritability succeeded in identifying when each applied, and why it did so, clearly that would constitute a major step forward. Possibly the research could do that provided there were good measures on the nature and extent of the environmental risks (as they varied either over time or within populations), provided it was possible to quantify the environmental mediation of those risks, and provided the choice of research design (and samples) allowed a focused contrasting of competing hypotheses. Those are tall orders and scarcely any of the studies even come close to meeting the requirements. Not surprisingly, therefore, the findings are rather contradictory and inconclusive. The interest in the effects on heritability of changes in social control or in the availability of opportunities is pertinent, but any adequate testing will require measures of these changes (together with measurement of alternative possibilities). Accordingly, although we are aware that distinguished researchers whom we respect are more positive about the overall strategy of studying variations in heritability than we are, we are unconvinced. Given that all the needed research requirements can be met (not an easy matter), it could constitute a strong research strategy. In their absence, however, it is a weak one.

Gene–environment correlations (rGE)

Passive, active and evocative types

Gene–environment correlations (rGE) concern genetic influences on individual variations in people's exposure to particular sorts of environments. This may come about through either the parents' genes or the child's genes. Obviously, these are connected but they work in somewhat different ways and they need to be examined through different approaches. Plomin et al. (1977) differentiated among 'passive', 'active' and 'evocative' rGE and we use the same distinctions. The term 'passive' rGE refers to the fact that the genetic influences on individual differences in environmental risk exposure are independent of actions of the individual child. The rGE comes about because the kind of rearing environment that parents provide will be influenced by their own behavioural characteristics (with respect, for example, to personality features, mental disorder, and intellectual qualities), and these characteristics are influenced by genetic (as well as environmental) factors. Epidemiological evidence is consistent in showing that there are strong associations between parental psychopathology and the family environments that they provide for the upbringing of their children (Murray & Cooper, 1997; Rutter, 1989b). For example, an early study compared the rates of family discord and of focused negativity on one of the children between families with a mentally ill parent and families in a comparable general population sample (Rutter & Quinton, 1984). It was found that family conflict and focused hostility were much more frequent in the families with a mentally ill parent. Of course, mental disorder in the parents will have been influenced by environmental as well as genetic factors but the evidence indicates that parental psychopathology is associated with an increased likelihood that parents will provide a risk environment for the children.

Passive rGE needs to be studied through twin studies of parents – so-called twin parent designs (Neiderhiser et al., 2004). The usual MZ–DZ comparison is simply applied to the phenotype of the rearing environment provided by the parent (in terms of negativity, conversational interchange, discipline, etc.). Sometimes this is misleadingly equated to a 'shared environmental effect' because what is being studied is a family-wide environmental factor. It is misleading because the 'shared environmental effect' is not concerned with whether or not the influence is within or outside the family, or even with whether it is a family-wide influence. Rather, it refers strictly to whether or not the environmental influence tends to make siblings more alike (if so, the effect is 'shared') or less alike (in which case it is 'non-shared') (Rutter, in press a; Rutter et al., 1999a; Rutter et al., 2001). It follows that passive rGE is concerned with a general parenting tendency but whether or not it gives rise to a 'shared' or 'non-shared' environmental effect will depend on the extent to which the general parenting tendency impinges equally on all children in the family. To the extent that it does not, the non-shared elements will derive from influences other than the passive rGE as such, but it cannot be assumed that passive rGE will affect all children in the same way or to the same degree.

'Active' and 'evocative' rGE are different in that they concern the child's genes. 'Active' rGE refers to the genetic effects on the child's behaviour that serve to select or shape the environments experienced. Thus, according to their interests and skills, some children will spend much of their free time reading, others will be out on the football field, some will be practising the violin or piano, and some will be chatting and playing with friends. That they choose to spend their time in a particular way will be affected by genetically influenced behaviours, attitudes and propensities. 'Evocative' rGE is different only in the sense that it refers to interpersonal effects rather than effects on non-social aspects of the environment. Thus, some children are fun to be with, but others tend to irritate or annoy and these tendencies will serve to shape how they are treated by other people.

Child-based designs of one kind or another are required to assess 'active' or 'evocative' rGE. Thus, the experiences of the child (such as stressful life events) are treated as the phenotype in twin studies. Alternatively, adoption designs may be used in order to determine if the genetic risks associated with the biological parents who did not rear the child are associated with effects on the rearing provided by the adoptive parents, these effects being mediated by the behaviour of the children (see Ge et al., 1996; O'Connor, Deater-Decksard, Fulker, Rutter, & Plomin, 1998).

rGE is sometimes used by behavioural geneticists in the more restrictive sense of a shared genetic liability that impinges on both the environmental risk factors and the phenotype being studied. Thus, Thapar, Harold, and McGuffin (1998) showed that the co-occurrence of life events and depression in young people in part reflected shared genetic liability (unfortunately such inferences are limited by the fact that data came from the same informants). Kendler and Karkowski-Shuman (1997) similarly showed that there was a shared genetic liability between major depression and liability to negative life events in adults. Silberg et al. (1999), using different informants, found a shared genetic liability to life events and depression in girls and an indication for an increasing heritability of depression in girls that became manifest during the adolescent age period. The implication was that a combination of rGE and $G \times E$ were bringing about, during adolescence, a greater exposure to, and sensitivity to, life events in females than was present in childhood (when the rates of depression in boys and girls were similar) (Eaves, Silberg, & Erkanli, 2003). A sibpair study in adults (Farmer et al., 2000) failed to find evidence for a common factor influencing both depression and life events, but this negative finding may have derived from sampling limitations and, in any case, because the focus was on sibpairs rather than twins, genetic influences could not be separated from environmental effects. Nevertheless, uncertainties remain on the extent to which this narrower concept of rGE operates. As discussed below, it is irrelevant for the basic question of whether or not genes influence individual differences in environmental risk exposure.

Range of environments affected by rGE

In considering the role of rGE in relation to the rearing environment, it may be helpful to note first the different types of questions that need to be examined, before turning to the differentiation of the three types of rGE and their respective roles in causative processes. The starting point has to be the evidence on the range of environments that are open to possible rGE effects (see Plomin, 1994; Plomin & Bergeman, 1991). It is clear that the range is very wide indeed. Kendler, Neale, Kessler, Heath, and Eaves' (1993) twin study findings showed a moderate heritability for most major life stresses, but not for those (such as deaths of friends or relatives or negative experiences in the person's social network) that are outside the person's control. Plomin, Lichtenstein, Pedersen, and McClearn (1990) similarly found that the heritability was greatest for controllable life events in late life; Billig, Hershberger, Iacono, and McGue's (1986) findings in adolescence were similar. More recent smaller studies of volunteer samples (Jang, Vernon, Livesley, Stein, & Wolf, 2001; Stein, Jang, Taylor, Vernon, & Livesley, 2002) have produced findings broadly pointing in the same direction. With respect to family features likely to affect rearing, genetic influences have been found to apply to most of those that involve the behaviour of the person on other people – such as marital difficulties and marital breakdown (Jockin, McGue, & Lykken, 1996; Kendler et al., 1993; McGue & Lykken, 1992), parent–child effects (Elkins, McGue, & Iacono, 1997), styles of parenting (Deater-Deckard, Fulker, & Plomin, 1999; Perusse, Neale, Heath, & Eaves, 1994), corporal punishment (Wade & Kendler, 2000) and interest and engagement in aptitude-based leisure activities such as religion or intellectual pursuits (Hur, McGue, & Iacono, 1996).

Personal qualities involved in shaping and selecting environments

The next question concerns the types of personal qualities that play a role in shaping and selecting environments. Kendler, Gardner, and Prescott (2003a), studying a population-based sample of over 7,000 adult twins, showed that neuroticism was associated with an elevated risk for marital problems, job loss, financial difficulties, and problems getting along with people in their social network, but not with the risk of being robbed or assaulted. The implication is that an individual's personality in adulthood plays a significant role in influencing exposure to some forms of environmental adversity

(as also found by Saudino, Pedersen, Lichtenstein, McClearn, & Plomin, 1997), that this is not the result of reporting bias, and that the association is largely mediated by a common set of familial factors that are partially environmentally mediated and partially genetically mediated.

Jockin et al. (1996) tackled much the same issue in their investigation of the mediators of the genetic effect on divorce. Again, personality features were found to play a role (accounting for 30% to 40% of the heritability of divorce risk).

Sometimes, however, the answer to this question has been unexpected. The Colorado Adoption Project examined the correlations between the Home Observation and Measurement of the Environment (HOME) and young children's cognitive scores (see Plomin, 1994). It might be assumed that parental IQ would be the obvious mediator but, in the event, that was found not to be the case, leaving it wide open as to just which parental characteristic was serving to influence the family environment.

Surprisingly, the question of the personal qualities involved in the shaping and selecting of environments has been the subject of very little systematic investigation. Yet, it remains a key issue and it warrants much further research.

Child characteristics associated with evocative effects

The third question poses a similar query with respect to the child characteristics that are associated with evocative rGE. An adoption design is required for this purpose. Thus, O'Connor et al. (1998) used the Colorado Adoption Project to examine the negativity shown by adoptive parents. It was found that levels of negativity were significantly higher when the adopted children had a biological mother with antisocial behaviour, and that this was mediated by the children's oppositional/disruptive behaviour. Ge et al. (1996) found much the same. The findings from the O'Connor et al. (1998) study, however, also showed that this evocative effect of the children's behaviour was also apparent in the children who were *not* at genetic risk because of their biological mother's characteristics. A quite different form of experimental design used by Anderson, Lytton, and Romney (1986) had earlier shown the same. It is clear that children's disruptive behaviour does influence how they are treated by their parents. rGE is involved to some degree but the evocative effect is evident irrespective of the presence of genetic risk (at least insofar as it can be indexed by biological parent characteristics).

Nevertheless, it remains unknown whether children's oppositional/disruptive behaviour constitutes the main mediator of evocative rGE because there has been so little research into this issue, and because other possible mediating child characteristics have not been studied. As with the parental mediators of the shaping and selecting of environments, this constitutes a research priority. Multivariate analyses in adult twin samples are needed to determine whether, for example, the genetic effects on divorce are primarily mediated through overt antisocial behaviour, some temperamental feature (such as neuroticism, impulsivity or sensation seeking), lack of religiosity, anxiety, depression or substance abuse – to mention but a few examples.

Rearing patterns affected by passive and evocative rGE

The fourth question focuses on the relative impact of passive and evocative rGE for different types of rearing pattern. Plomin et al. (1977) argued that a direct measure of passive rGE was obtainable from comparison of the correlation between the family environment and the child phenotype in adoptive and biological families (see also Plomin, 1994). It is important to note, however, that this is only the case if the range of environments, and particularly the proportion of high-risk environments, is similar in the two sorts of families. Subsequent data have made it clear that this is very rarely the case, at least with respect to the types of risk environment involved in susceptibility to emotional and behavioural psychopathology (Rutter et al., 1999a, 2001; Stoolmiller, 1999). The offspring of twins design provides a somewhat more satisfactory way of tackling the question (D'Onofrio et al., 2003; Silberg & Eaves, 2004). In brief, the rationale is that the children born to identical twin mothers (or fathers) are half-siblings rather than cousins as they would be if their mothers were sisters or dizygotic twins, rather than monozygotic twins. By focusing on this contrast, it is possible to determine the extent to which the genetic identity of the monozygotic sisters (as compared with pairs of dizygotic sisters) leads them to produce similar rearing environments. It is also clear that the design provides a means of testing for environmental mediation of the effects of the rearing environment on the children's behaviour. The one key limitation, of course, is that the fathers who have married the monozygotic twin mothers will be unrelated and therefore there will be an influence coming from this other parent. The design has been little used in studying either gene–environment correlations or environmental mediation up to now (however, see Jacob et al., 2003), but there are several studies in the pipeline that are doing so to good effect.

Neiderhiser et al. (2004) sought to differentiate between passive and active/evocative gene–environment correlations in adolescence by using a combination of a child-based design (a sample of same-sex twin and sibling pairs) and a parent-based design (a sample of 326 twin pairs who were mothers of adolescents). The same measures of parental positivity, negativity, control and monitoring were used in both

samples. The findings were interesting with respect to the indication that passive rGE was influential for maternal positivity and mothering, but that active/evocative rGE was more operative for maternal negativity and control. Caution is required in drawing conclusions, however, because of the generally low correlations among the parent, child and observer measures and because of the somewhat different findings according to reporter. On the whole, genetic effects were greater on maternal than on child reports and were scarcely evident on observer measures. The importance of examining rGE in relation to different aspects of parenting is even more strongly evident in the findings of Jaffee et al. (2004) using the Environmental Risk Longitudinal Study of 1,116 British 5-year-old twins followed from birth. Evocative rGE was evident for parental corporal punishment, accounting for a quarter of the variance – a proportion similar to Wade and Kendler's (2000) estimate based on maternal retrospective reports. By contrast, there was no rGE for physical maltreatment. With both, shared environmental effects predominated. It is relevant, however, that although most children who experienced corporal punishment were not maltreated, their risk for maltreatment was increased two and a half times over the base rate. The association between the two was environmentally determined from the child's perspective; that is, it was not influenced by the child's genes. A parent-based design would be needed to test if parental genes influenced the liability to maltreat the children.

rGE and environmentally mediated risks

The next issue concerns the assessment of environmentally mediated risk mechanisms in the presence of rGE – of either the passive or evocative varieties. If the parenting feature that might affect rGE is measured as a family characteristic, rather than in terms of child-specific impact, two research designs may be employed to test for the environmental mediation of risk – the offspring of twins design (as described above) and the extended twin-family design (see Meyer et al., 2000 for the rationale, the assumptions required, and the limitations). In essence, this relies on having measures of the same phenotype in the parents as is being studied in the children. By utilising the correlation between the parental phenotype and the postulated risk environment for the children, and doing so within a twin design, it is possible to separate genetic and environmental mediation. The strategy has been used to show the environmentally mediated risk effects of family maladaptation on children's antisocial behaviour (Meyer et al., 2000), and the effects of parental loss in childhood on alcoholism in adult life (Kendler et al., 1996). However, the extended twin-family design involves several unwieldy conceptual and statistical assumptions (see Meyer et al., 2000). For example, it is assumed that everything at the child level applies equally at the parent level and that the additive genetic effects correlate .5 across generations in keeping with the .5 correlation between siblings or dizygotic twins (the genetic relationship between parent and child being the same as that between siblings). Empirically, these assumptions have often been found not to be borne out.

At one time, behavioural geneticists implied that it was possible to include measured family-wide risk factors in the modelling of genetic and environmental effects on population variance, thereby quantifying the environmental effects of the risk factor (Miller, Mulvey, & Martin, 1996, 2001). In fact, as pointed out by Turkheimer et al. (in press), it is not possible to do this in a way that takes account of possible genetic mediation. That is because partitioning of the genetic and environmental variance of a measured putative environmental risk factor has to rely on differences *within* twin pairs. If there is no between-twin difference on the risk variable (as measured), that rules out the approach. Of course, that does not mean that there will be no environmental effect of a family-wide risk factor. Numerous studies have shown significant shared environmental effects and there is a range of varied research designs that can test for environmental mediation of risk (Rutter et al., 2001). All have a mix of strengths and limitations and the way ahead lies in using multiple research strategies because the designs differ in their particular mix of pluses and minuses.

Because of the conceptual and technical problems involved in dealing with a family-wide environmental feature (such as family discord or parental education), it is desirable to break it down into some aspect that can be conceptualised and measured in a twin-specific fashion. If the impact is very similar in both twins, the analysis will show a substantial shared environmental effect (see Pike, McGuire, Hetherington, Reiss, & Plomin, 1996) but the analytic problems are much less than with a risk factor measured only on a family-wide basis.

In essence, if the parental feature can be measured separately for each twin, there are two main analytic designs possible. First, the environmental risk effect can be tested within monozygotic pairs (who do not differ genetically) – as shown for negative expressed emotion (Caspi et al., 2004). Second, it can be assessed through cross-twin, cross-trait analyses (in which the environment is treated as one of the traits to be examined). The already noted Pike et al. (1996) study of parental negativity provides an example of this kind. It is clear that hypotheses about environmentally mediated risks can be tested even in the presence of rGE, with findings demonstrating important environmental risk effects (Rutter, 2005).

Modelling the overall effects of rGE

The final issue concerns the overall effects of rGE in relation to the risks for child psychopathology. This

has been modelled for rGE in relation to the risks for depression in both adolescent girls (Eaves et al., 2003) and adult women (Kendler, Gardner, & Prescott, 2002). Both sets of findings showed that an important portion of the risk derived from the role of rGE in affecting the likelihood that individuals would experience risk environments. However, neither quantified the strength of this effect.

Ge et al. (1996) modelled the role of evocative rGE in their adoption study of 41 adoptees aged 12 to 18 years, the sample having been chosen to provide a contrast between those who had a biological parent with substance abuse, alcohol abuse or antisocial personality, and those whose biological parents had none of these three disorders. Path analysis showed an effect of the biological parentage on the adoptees' antisocial/disruptive behaviour which, in turn, showed a reciprocal mutual influence effect on the adoptive mother's harsh/inconsistent discipline, with the last also showing a significant effect from the adoptive parents' marital warmth (which was unassociated with the qualities of the biological parents). The analyses point to a significant contributory role of evocative rGE, but with negative parenting also independently associated with the quality of the marital relationship, and negative parenting influencing, as well as being influenced by, the children's behaviour. The sample size was quite small and causal inferences are uncertain in view of reliance on cross-sectional data. However, the approach indicates the kind of modelling that can be undertaken.

These modelling findings necessarily had to deal with unmeasured, unidentified genes and it might be supposed that the effects of rGE should be able to be investigated on a much surer basis once the relevant genes for risk environments have been found. That is not the case, unfortunately. The term 'gene–environment correlation' seems to imply that the genes are having an effect on the environment but, of course, that is not actually what is occurring. Rather, the genes are having effects on behaviour and it is the behaviour (of the parent or the child) that is shaping the environment. To search for genes coding for specific environments would be a totally misguided enterprise. It is noteworthy, for example, that despite the importance of rGE, none of the measured genes involved in G × E (see section below) showed a significant, or even substantial, association with the risk environments studied. Rather, attention needs to be paid to identification of the specific child or parental behaviours that serve to influence environments and then, only secondarily, search for the genes that provide susceptibility to those behaviours.

Conclusions on rGE

Two main conclusions on rGE are evident. First, through passive, active and evocative rGE, part of the genetic influences on child psychopathology derive from genetic effects on individual differences in the likelihood of children experiencing a risk environment. Second, part of the risk associated with adverse environments is mediated genetically, rather than environmentally. A proper understanding of psychopathological risk processes is dependent on the delineation and quantification of both effects. As discussed, twin and adoptee designs have a crucial role to play in such research. Nevertheless, a shift of focus will be needed in order to examine the mechanisms involved in the effects on environments of parental behaviour (with respect to passive rGE) and of children's behaviour (with respect to active and evocative rGE).

Gene–environment interactions (G × E)

During the era of the 1980s to early 1990s, the generally accepted view in behavioural and psychiatric genetics was that gene–environment interactions (G × E) were rare, and of such limited importance that they could be ignored in most circumstances. This dismissal of G × E arose from two main considerations. First, this early period of the application of molecular genetics to psychiatric disorders was predicated on the dual assumption that, in most instances, the genes would have relatively direct effects on disorder, and that the effects of multiple susceptibility genes on a disorder would be additive rather than synergistic. The 'direct effect' assumption was a carry-forward of what had worked in the case of single gene Mendelian disorders, with the expectation that something of the same kind might apply in the field of psychiatry. To begin with, the hope was that complex mental disorders would turn out to be caused by multiple different single gene conditions (Kidd, 1991). However, even when it became clear that that was unlikely to be the case, other than rarely, the assumption of relatively direct effects continued. Hence, there was much talk of the possibility of discovering the genes 'for' various psychiatric conditions. As Kendler (2005b) has pointed out, all the susceptibility genes for multifactorial disorders that have been discovered so far have been found to have very slight effects. That finding alone makes it rather unlikely that the causation would have the directness that the 'genes for' terminology implied. The approach also ignored the evidence from the rest of medicine that many risk factors operated on the basis of dimensional characteristics (Rutter, 2003) and that there were often multiple pathways to the same disease end point (Rutter, 1997). It should be no surprise, therefore, that the susceptibility genes found so far for mental disorders do not involve a pathogenic effect that knocks out a vital function, but rather represent particular allelic variations of common genes. We are only just at the beginning of the phase of being able to understand just what these

genes do, but the likelihood is that they affect particular physiological pathways that make a psychiatric condition more or less likely, but the genes do not cause a mental disorder at all directly.

The assumption that genetic effects are ordinarily additive has led to a view that the reductionist strategy of studying genes without reference to environmental effects should be useful (Colhoun, McKeigue, & Davey Smith, 2003). That may well be the case in some instances, but it does seem an odd assumption to make. The implication would have to be that, even when multifactorial disorders involve both strong genetic and strong environmental effects, the two are completely independent from one another and do not operate through the same causal pathway.

The second reason for dismissing G × E arose from quantitative genetic 'black box' analyses of anonymous (i.e., unmeasured) G and anonymous E, which usually failed to show G × E (Plomin, DeFries, & Fulker, 1988). It is important to appreciate that what is being tested for here is an omnibus interaction between all genes and all environments. Such an interaction seems biologically implausible and, accordingly, it is not at all surprising that such G × E has rarely been found. The biological evidence is of genetically influenced sensitivities to specific environments, and it has been usual to find that such sensitivities often apply only to minority subgroups of the overall population (Rutter & Pickles, 1991; Rutter & Silberg, 2002).

There are two further subsidiary reasons for rejecting this behaviour genetic dismissal of the operation of G × E. First, the testing has been for a multiplicative interaction, meaning one that operates on a logarithmic scale (Rutter, 1983; Rutter & Pickles, 1991), and this concept of interaction does not necessarily coincide with the ways that genes and environments actually interact in nature (Yang & Khoury, 1997). The second consideration is that statistical interaction requires variations in *both* G and E. If the E that creates risk is all-pervasive there cannot be a multiplicative interaction, even if the reality is that the effects of G are wholly contingent on E. Many of the best-known examples of G × E in medicine involve pervasive environmental risk, and therefore would not pass the test of multiplicative interaction (Moffitt et al., in press). Thus, environmental risks are pervasive in the case of genetically moderated susceptibility to malaria in regions where that infection is endemic, genetically moderated allergic reactivity to airborne spring pollens, and genetically determined phenylketonuria in response to ordinary diets. In these examples, genes moderate people's capacity to resist the health-damaging effects of a pathogenic environment, even when that environment lacks variation in the population under study.

There is good reason, therefore, to doubt assumptions about the rarity of G × E. However, there are also positive reasons to consider that G × E might be both common and important (Moffit, Caspi, & Rutter, 2005, in press: Rutter, in press a). First, there is the basic underlying evolutionary concept of natural selection. This argues that genes are involved in the adaptation of organisms to their environment, that all organisms in a species will not respond to environmental conditions in the same way, and that this within-species variation in response involves individual differences in genetic endowment. In short, genetic variation in response to the environment is the raw material for natural selection (Ridley, 2003).

Second, biological development at the individual level involves adaptations to the environmental conditions that prevail during the formative period of development (Bateson & Martin, 1999; Bateson et al., 2004; Gottlieb, 2003). The literature on biological programming as a result of early experiences provides relevant examples (Rutter, in press b). Given that human development is an environment-dependent process, it is implausible that genetic factors do not play a role in moderating that process (Johnston & Edwards, 2002). It is even more implausible that the process does not include mental health and mental disorder among its outcomes.

Third, both human and animal studies are quite consistent in revealing great variability in individuals' behavioural responses to all manner of environmental hazards (Rutter, in press c). A heterogeneity in response characterises even the most overwhelming of traumas, including all known environmental risk factors for psychopathology. To suppose that such response heterogeneity is not influenced by genes would require some assumption that although genes influence all other areas of biological and psychological function, responsiveness to the environment is uniquely outside the sphere of genetic influence (Moffitt et al., in press; Rutter, in press a). Up to now, there has been relatively little direct study of genetic influences on susceptibility to particular environments, but there is the beginning of evidence of their operation (Kotb et al., 2002; Uhart et al., 2004). It is also the case that research guided by resilience concepts shows that individual variation in response to environmental hazards is associated with pre-existing individual differences in temperament, personality, cognitive functioning and psychophysiology, all of which are known to be under a degree of genetic influence (Rutter, in press c).

Finally, the fourth reason for expecting G × E in the field of mental disorder is that there is a rapidly growing body of evidence of its importance in somatic medicine (Moffitt et al., 2005, in press; Rutter, in press a). For example, in the study of cardiovascular disease, subjects in the Framingham Heart Study who had high dietary fat intake developed abnormal HDL cholesterol concentrations, or did not, depending on their genotype on the polymorphic hepatic lipase (HL) gene promoter

(Ordovas et al., 2002). This HDL G × E has been replicated (Tai et al., 2003). A separate study showed that tobacco smokers developed coronary heart disease, or did not, depending on their lipoprotein lipase genotype (Talmud, Bujac, & Hall, 2000), and their apolipoprotein E4 (APOE4) genotype (Humphries et al., 2001). The APOE4 G × E has been replicated (Talmud, 2004). In the study of stroke-prone hypertension, rats exposed to a high-salt diet developed elevated systolic blood pressure, or did not, depending on their genotype on the polymorphic angiotensin-converting enzyme (ACE) gene (Yamori et al., 1992). Sayed-Tabatabaei et al. (2004), in the Rotterdam Study of people aged 55 years or older, found the d-allele variant to be associated with a significant increase in carotid artery thickness in smokers but not in non-smokers or ex-smokers, the G × E interaction being significant.

In a study of low infant birth weight, women who smoked tobacco during pregnancy gave birth to underweight infants, or did not, depending on their genotype with respect to two polymorphic metabolic genes, CYP1A1 and GSTT1 (Wang et al., 2002). In the study of dementing illnesses, patients with a history of head injury developed Alzheimer's dementia, and increased beta-amyloid deposition in the brain, or did not, depending on which allele of the polymorphic apolipoprotein (APOE) gene they possessed (Mayeux et al., 1995; Nicholl, Roberts, & Graham, 1995). This G × E pattern also applied when instead of head injury, the environmental influence on cognitive decline was oestrogen therapy (Yaffe, Haan, Byers, Tangen, & Kuller, 2000). In the study of dental disease, heavy tobacco smokers developed gum disease, or did not, depending on their genotype on the polymorphic interleukin 1 (IL1) gene (Meisel et al., 2002). This G × E has been replicated (Meisel et al., 2004).

In summary, the traditional notion that strictly additive, non-interactive, effects for genetic and environmental influences would constitute the norm must now be rejected. That is not to say that in some instances (perhaps many instances) the environmental influences on psychopathology will operate through entirely different causal pathways than those involved in genetic effects, but it does not seem probable that that will generally be the case.

The only really satisfactory way of finding a synergistic interaction between an identified susceptibility gene for some mental disorder and a measured environmental risk factor that has been shown to convey environmentally mediated risk is to use molecular genetic methods. Leads on the likelihood of there being a true gene–environment interaction can come from two sources. First, although G × E may apply in any multifactorial mental disorder, it is perhaps most likely when certain criteria apply. There should be evidence of important substantial environmentally mediated risks but, equally, there should be marked heterogeneity in people's vulnerability to such risks with respect to the probability of their developing the disorder in question. In addition, there should be evidence of a substantial genetic effect but also indications that such risks may operate in relation to indirect risk pathways rather than through a direct connection with a particular psychiatric condition. The level of heritability is not a major consideration but gene–environment interaction may be more probable when there is substantial discordance within monozygotic pairs.

The second source for anticipating the likelihood of G × E is the evidence from twin and adoptee studies. Necessarily, the implication of G × E is much less secure than with molecular genetic findings and there is the serious limitation that the interactions that can be studied have to deal with anonymous genes rather than with identified susceptibility genes. Nevertheless, they do provide a reasonable basis for anticipating true G × E.

Three groups of disorders fulfil these criteria: anxiety/depressive disorders, antisocial behaviour substance use disorders, and schizophrenia. As, in each of these three cases, there is good molecular genetic evidence, the findings will be discussed under these three broad diagnostic headings.

Anxiety/depressive disorders: quantitative findings

Genetically sensitive designs have shown various environmentally mediated effects from specific risk environments for anxiety/depression (Rutter, 2005). Kendler, Karkowski, and Prescott (1999) have shown this with respect to negative life events; and Pike et al. (1996) have shown it with respect to family discord and negativity. The heritability of depressive disorders is around 40% to 50% (Sullivan, Neale, & Kendler, 2000), although it may be higher than that for recurrent depression and for the more severe varieties of depression referred to tertiary care psychiatric centres (Kendler, 1997; McGuffin, Katz, Watkins, & Rutherford, 1996). The moderate level of heritability reflects the fact that there is considerable discordance within monozygotic pairs. There is less evidence on the heritability of anxiety disorders, but the heritability is unlikely to be higher than that for depressive conditions (Eley, Collier, & McGuffin, 2002). The twin evidence also indicates that there is substantial shared genetic liability between generalised anxiety disorders and depression (but with phobias being rather separate – Kendler et al., 1995b) and that, in both cases, much of the liability may be mediated via the personality trait of neuroticism (Kendler, 1996). In addition, multivariate modelling of twin data has shown that part of the genetic mediation is via effects on the likelihood of experiencing risk environments and the susceptibility to such environments (Eaves et al., 2003; Kendler et al., 2002).

Quantitative genetic studies have provided several pointers to the likelihood of G × E. Kendler et al.

(1995a) devised the ingenious strategy of using twin data to infer genetic liability at the individual level. Roughly speaking, the logic was that (dealing with the outcome of depressive disorder in early adult life) the highest genetic liability could be inferred in cases where the co-twin of an indexed twin with depressive disorder had also suffered from a depressive condition. That is, because they shared all their genes, it seemed reasonable to conclude that the occurrence of the depressive disorder in the co-twin was likely to have been strongly influenced by genes. Conversely, the lowest genetic liability was inferred in the case of a monozygotic co-twin of an indexed twin with depressive disorder, who did not have a history of a depressive condition. The argument here was that if, despite being a member of a monozygotic pair, the co-twin had escaped developing depression, the genetic liability was likely to be low. Using a similar logic, dizygotic pairs could be inferred to be somewhere in the middle. What the findings showed was that the likelihood that a co-twin would develop the onset of a new depressive disorder following a serious negative life event was greatest in the presence of a high genetic liability and lowest when there was low genetic liability. The clear implication was that at least part of the genetic effect was operating through effects on genetic susceptibility to risk environments.

Silberg, Rutter, Neale, and Eaves (2001) used a twin design in a different way to examine the depression-inducing effects of stressful life events. Attention was confined to life events (LE) not showing rGE focusing on adolescent twin girls in the Virginia Twin Study of Adolescent Development. The findings showed a significant increase in heritability in the presence of LE, an increase that was entirely due to the presence of G × E. The phenotypic analysis showed no effect of LE on anxiety or depression in the absence of a genetic risk, but a significant effect in its presence. On the other hand, genetic factors did have a significant effect in the absence of LE, indicating that there must have been effects on susceptibility to depression and anxiety that operated other than through susceptibility to risk environments (or alternatively that the range of risk environments that were operative were not included in those studied in the investigation).

Eley et al. (2004a) used longitudinal family data from two ongoing genetic studies (with a combined sample of 1,818 adolescent offspring) to examine the possible interplay between familial vulnerability (as indexed by questionnaire measures of anxiety, depression and neuroticism) and three environmental variables (parental education, social adversity, and negative life events) as predictors of a self-report questionnaire measure of adolescent depression one year later. A significant interaction between low parental education and familial vulnerability was found. As the authors noted, although the finding is of interest, caution is needed in view of sampling and measurement limitations. In terms of implications for possible G × E, it is also a limitation that the key 'environmental' risk factor concerned a distal, rather than proximal, risk, with uncertainty on what was the operative risk feature of the environment.

The same two studies were used by Lau and Eley (in press) to test for possible G × E, using a twin and sibling design (rather than a parent–offpsring design). Negative life events and maternal punitive discipline were used as environmental risk indices, both of which involved some genetic influence, requiring appropriate modelling to take account of rGE, using an approach developed by Purcell (2002). As with the earlier Silberg et al. (2001) study described above, G × E was inferred from the increase in genetic variance with increasing environmental risk.

Although the quantitative genetic findings on G × E are quite limited, they are consistent in pointing to the likelihood of G × E, as do the other findings on the mode of operation of genetic and environmental effects on anxiety and depression.

Anxiety/depressive disorders: molecular genetic and measured environment findings

Against that background, Caspi et al. (2003) decided to focus on the possibility of G × E in relation to the environmentally mediated effects of maltreatment and stressful life events on depression, in relation to a functional polymorphism in the promoter region of the serotonin transporter gene. Lesch et al. (1996) had earlier reported that the short allele version of this gene was associated with a significant effect on the risk of depression. In the years that followed, several other investigators failed to replicate this positive finding for a possible susceptibility gene that operated in relation to depression (Lesch, 2003). Caspi et al. (2003) argued that there was substantial evidence implicating the possible role of serotonin in the liability to depression and they hypothesised that the lack of replication might derive from the susceptibility effect of this allelic variant being dependent on G × E (Caspi et al., 2003). The Dunedin Longitudinal Study was used to test the G × E hypothesis, using both informant and self-report measures of depression. The findings showed a significant main effect of both maltreatment in childhood between the ages of 3 and 11 years and stressful life events between the ages of 21 and 26 years (assessed through a reliable life history calendar) prior to the onset of depression in late adolescence/early adult life, but no significant main effect for the serotonin transporter gene (both findings being in keeping with prior research). What was new was the evidence of a significant and substantial G × E effect. The investigators tested the alternative possibility that the interaction represented G × G, rather than G × E, by testing for the interaction with the serotonin transporter gene in relation to life

events occurring after the onset of depression. If there truly was G × E, it could not apply to life events after onset whereas G × G should be unaffected by the timing of the life events. The lack of an interaction with post-onset life events supported the G × E, rather than G × G, inference. The specificity of the genetic effect was tested by checking whether the G × E found earlier with respect to an MAOA gene and childhood maltreatment applied to depression. The findings showed that it did not (Caspi et al., 2002).

Eley et al. (2004b) used a sample of adolescents aged ten to twenty years to test for the interaction found by Caspi et al. (2003). Depression was measured by the self-report Mood and Feelings Questionnaire and environmental risk was assessed through another questionnaire including threatening life events that impinged on the parent or family as a whole. The sample was subdivided into four quadrants according to high or low depression and high or low environmental risk. As in the Caspi et al. (2003) study, there was a significant interaction between the short allele variant of the serotonin transporter gene and high environmental risk, but only in girls. The lack of a significant G × E effect in males is difficult to interpret because, as one would expect, the proportion of males with a high depression score was very much lower than the proportion of females. It was noteworthy, too, that in the low environmental risk group, the short allele variant was associated with a *lower* rate of depression. This disordinal interaction affect awaits replication but it would be in keeping with the evolutionary notion that the interaction reflects environmental reactivity rather than just susceptibility to environmental adversity. That is, high reactivity phenotypes might be disproportionately found in *both* highly stressful and highly protected early social environments (Belsky, 2005: Boyce & Ellis, 2005; Ellis, Essex, & Boyce, 2005). Like Caspi et al. (2003), Eley et al. (2004b) found no G × E effect on depressive symptoms with respect to the MAOA genetic variant that showed G × E with respect to maltreatment in relation to antisocial behaviour (see below).

Kendler, Kuhn, Vittum, Prescott, and Riley (2005) used the Virginia adult twin study to determine whether they could replicate the G × E finding of Caspi et al. (2003). Both depression and life events were assessed through standardised interview measures. The same significant interaction was found with respect to the short allele variation and stressful life events but this applied only in relation to commonly occurring mild/moderate threat events, rather than the rarer high threat events. The genotype had no effect on generalised anxiety either as a main effect or as an interactive effect. The finding that the G × E applied only to lower-level threat events is both puzzling and intriguing, but it awaits replication.

Grabe et al. (2005) tested for the same G × E in a general population sample in Germany with a mean age of 52 years. A self-report questionnaire was used to assess mental and physical distress and environmental risk was assessed in relation to unemployment and lack of social support for the individual. The G × E with respect to the serotonin transporter gene was significant in females, but not in males. As the authors noted, the relevance of the replication of G × E for females is strengthened by the fact that the sample characteristics and risk structure were so different from those used in earlier studies.

Kaufman et al. (2004) tested for the G × E in a small sample of 57 children removed from their parents' care because of maltreatment and 44 community controls. There was a mean age of ten years. Children homozygous for the short allele variant had a higher depression score on the Mood and Feelings Questionnaire only in the maltreated group. It was notable, too, that the presence of social support also reduced the G × E effect. The findings are limited by the small sample size and the lack of longitudinal data but, as with the Kendler et al. (2005) findings, the implication is that any adequate understanding of G × E is likely to require discriminating environmental measures of both possible risk and protective factors.

Two further confirmations have recently been reported. Wilhelm et al. (in press) studied a longitudinal cohort of 165 young adults, finding a significant interaction between the short allele genotype and adverse life events with respect to the occurrence of major depression; and Zalsman et al. (in press), studying 191 participants with a mood disorder and 125 healthy volunteers (both aged in their 30s), found a similar G × E interaction with respect to life events on the severity of depression, but also a main effect of the same genotype.

Fox et al. (in press) studied G × E in a longitudinal study of behavioural inhibition as assessed at 14 and 84 months in a sample of 153. A lack of social support was used as the environmental risk and the short allele–long allele contrast was used as the genetic influence. Controlling for behavioural inhibition at 14 months, 5HTT genotype status related to the 84-month shyness score and behavioural inhibition as observed when there was low social support but not when there was high support (when it had the reverse effect). The finding is in keeping with the general pattern of other results on G × E in relation to the 5HTT genotype, but caution is needed in view of the outcome on temperament (which differs from the other studies) and in view of the disordinal interaction.

Manuck, Flory, Ferrell, and Muldoon (2004) investigated whether the genotype interacted with socio-economic status in the effect on serotonergic responsivity as assessed by a fenfluramine test in 139 adult men and women. The short allele variant

of the serotonin transporter gene showed a significant interaction with socio-economic status, there being no SES effect in individuals who are homozygous for the long allele version.

So far, the one total failure to replicate is the study by Gillespie, Whitfield, Williams, Heath, and Martin (2005) in their study of 1,099 adults from the Australian volunteer twin register. They found a significant main effect on depression for stressful life events but no significant effect for genotype or for G × E. The study was a good one and it is not clear why, in contrast with the other studies, there was a failure to replicate the G × E. The authors discussed various limitations in their study, including the very much broader (and higher) age range of their sample, but it remains unclear why the findings are different.

Taken overall, especially given the weaker statistical power for the detection of the interactions as compared with main effects (McCall, 1991; Wahlsten, 1990), the proportion of positive replications of the Caspi et al. (2003) findings on G × E is impressive. However, if the G × E reflects an important biological mechanism, other research strategies on the biology ought to confirm the effects of the gene on physiological responses to stress. That has been the case in research with both humans and other animals (Moffitt et al., in press). Thus, Hariri et al. (2002, 2005), using a functional brain imaging strategy, showed that humans with a short copy of the serotonin transporter gene exhibited greater amygdala neural activity to fearful visual stimuli than did individuals who were homozygous for the long allele. Heinz et al. (2005) confirmed this effect. Battaglia et al. (2005) found that children with one or two copies of the short allele variant of the serotonin transporter promoter gene had a smaller cerebral visual event-related potential following exposure to overtly hostile and neutral facial expressions. The implication is that there was an effect on amygdala activation. Monkey studies, too, have shown that the same short allele was associated with a differential response to adverse rearing as shown by serotonin metabolites in the cerebral spinal fluid (Bennett et al., 2002), by visual orientation to stimuli (Champoux et al., 2002) and by increased ACTH levels (Barr et al., 2004). In addition, Murphy et al. (2001), using a gene knock-out model in mice, found a difference in hormonal responses to stress according to the serotonin transporter gene. These consistent findings on the likely biological underpinning of the G × E with respect to the serotonin transporter gene means that it is highly probable that the interaction does indeed reflect an important biological mechanism.

Antisocial disorders/substance misuse: quantitative findings

Antisocial behaviour has been shown to have environmentally mediated risks from specific adverse environments (Rutter, 2005) as shown by twin designs (Pike et al., 1996) and by longitudinal studies that provided the opportunity to test for an environmental mediation (Costello, Compton, Keeler, & Angold, 2003; Laub, Nagin, & Sampson, 1998; Zoccolillo, Pickles, Quinton, & Rutter, 1992). In all cases there has been marked heterogeneity in people's responses to the risk environments, and twin and adoptee studies of various kinds (see below) have shown that the effects are mainly evident in young people who are at genetic risk. The heritability of antisocial behaviour is about 50% (Moffitt, 2005) along with substantial discordance within monozygotic pairs. The evidence on heritability of substance use and abuse is less consistent but there is moderate to high heritability for persistent substance abuse (although much less for the initiation of use of substances) (Ball & Collier, 2002; Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995a, 1995b; Krueger et al., 2002). There is substantial overlap in the genetic liability for antisocial behaviour and substance use problems, as well as with temperamental features and attention deficit/hyperactivity disorder. Although there is a lack of clear evidence on the mediating pathways for genetic effects, the implication is that the effects are not diagnosis specific.

The initial pointers that G × E was likely to be operating in some forms of psychopathology came from adoption and twin studies (summarised in Rutter & Silberg, 2002 and Tsuang et al., 2004). Thus, Cadoret, Cain, and Crowe (1983), in a study of 367 adoptees, found a significant G × E such that there was a negligible risk for antisocial behaviour from a genetic factor alone (as crudely indexed by antisocial behaviour in the biological parent), no effect from an adverse adoptive family environment alone, but a substantial effect when both were present. More recently, Cadoret et al. (1995a) studied some 2000 adoptees, using antisocial personality disorder in a biological parent as an index of genetic risk, and a range of features (such as marital problems, alcohol/drug problems, or divorce/separation in the adoptive parents) as a measure of an adverse rearing environment. Again, a significant G × E was found. 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; however, the findings in males were negative. A similar pattern of an apparent G × E synergism was evident in studies by Cadoret, Troughton, and O'Gorman (1987) and Bohman (1996), although in both cases the numbers in the G + E cell were too small to detect a statistically significant effect. In a different adoptee study, Crowe (1974) had found that early institutional care was a risk factor for later antisocial behaviour only when a genetic risk factor was present.

Sigvardsson, Bohman, and Cloninger (1996), in two Swedish adoption studies, found that the rate of alcohol abuse was twice as high when there was both genetic risk and environmental risk as compared with either on their own (neither of the latter differed from controls). A rather smaller American adoptee study of alcohol abuse (Cutrona et al., 1994) found a significant (but weak) interaction between alcoholism in the biological parent and conflict in the adoptive family in women but not in men.

Jaffee and colleagues (2005) used the Kendler et al. (1995a) twin design that inferred genetic liability from the pattern of MZ–DZ concordance to examine G × E with respect to child maltreatment and the development of antisocial behaviour. Significant G × E was found, with the implication that part of the genetic effect on antisocial behaviour operated through influences on susceptibility to the ill effects of child maltreatment.

These twin and adoption findings are important and persuasive of the likelihood of G × E for both antisocial behaviour and substance use/misuse. Although there is a substantial association between antisocial behaviour and substance use/misuse (see Rutter, 2002), it is unlikely that the G × E will operate in the same way. Substance use/misuse constitutes a good candidate for molecular genetic investigations of G × E if only because the psychopathology is defined in terms of a known environment risk factor – namely, use of alcohol or other substances (Heath & Nelson, 2002). The genetic susceptibility, however, might involve either liability to engage in risk-taking behaviour (such as taking drugs) or psychophysiological response to particular substances. In view of the present state of knowledge, therefore, we restrict our discussion of G × E in relation to identified genes to antisocial behaviour.

Antisocial disorders: molecular genetic and measured environment findings

Given the extent of pointers to the likelihood of G × E for antisocial behaviour, Caspi et al. (2002) went on to use molecular genetic methods in the Dunedin Longitudinal Study. Maltreatment was selected as the environmental risk factor because of the extensive evidence that it is associated with a markedly increased risk for antisocial behaviour but with considerable variability in response (Rutter, Giller, & Hagell, 1998; Widom, 1997). It was also selected as the environmental risk factor because of the evidence that it has lasting neurochemical correlates in both humans and animals. Standardised interview data were used to designate severe maltreatment (which applied to 8% of the sample of boys) and probable maltreatment (affecting 28% of the sample, the maltreatment having been experienced between the ages of 3 and 11 years). Individual differences in a functional polymorphism in the promoter region of the Monoamine Oxidase A (MAOA) gene was used for genetic susceptibility. The MAOA enzyme metabolises neurotransmitters such an norepinephrine, serotonin and dopamine – for which there is animal and human evidence of possible association with aggression. Antisocial behaviour was the outcome studied – being assessed through a range of categorical and dimensional measures using questionnaire and interview data, plus official records.

Results showed that the maltreated children whose genotype conferred low levels of MAOA expression more often developed conduct disorder, antisocial personality and adult violent crime than children with a high activity MAOA genotype. As with their parallel serotonin transporter gene study (see above), a variety of methodological checks were undertaken to test the validity of the finding. Thus, they tested whether the G × E applied to a range of different measures that shared construct validity – including the diagnosis of conduct disorder, a scale of conduct problem symptoms, a personality feature (aggressive personality) and an official crime record. As with the depression findings, the G × E applied across a range of measures tapping the same basic construct but having different scaling properties. They further argued that if the MAOA interaction with maltreatment was a consequence of scaling characteristics, a random SNP with similar allele frequencies ought also to show an interaction with maltreatment predicting conduct problems. It did not (Moffitt et al., in press). Similarly, if the interaction was a scaling artefact, it ought to predict an outcome having no relationship to the hypothesis but having the same prevalence as conduct disorder. Gum disease met that criterion and it did not show G × E. Because the serotonin transporter gene had shown an interaction with maltreatment in the liability to depression, Caspi et al. (2003) tested whether the serotonin transporter gene also showed G × E between maltreatment and antisocial behaviour. It did not.

Foley et al. (2004) replicated the finding using the Virginia twin study for adolescent behavioural development. Conduct disorder was assessed using standardised interviews of both the twins and their parents. Family adversity was defined in terms of interparental violence, parental neglect and inconsistent discipline as assessed by interview data from the children and the parents. As with the initial Caspi et al. (2002) study, the findings showed no main effect for the gene, a main effect for adversity but a substantial and statistically significant G × E. The study extended the Caspi et al. (2002) analysis by showing that the G × E could not be accounted for by either a passive or an evocative gene–environment correlation.

Haberstick et al. (2005), using the national Longitudinal Study of Adolescent Health sibling pair sample, found, as in the other two studies, that maltreatment (assessed using a six-item retrospective self-report questionnaire) predicted an aggregate

measure of conduct problems, that there was no main effect of genotype on conduct symptoms, and that the MAOA genotype was unrelated to individual differences in exposure to maltreatment. However, the G × E effect was far smaller than in the Caspi et al. (2002) study and fell well short of statistical significance. The environmental risk measures were less detailed than in the Caspi et al. (2002) study, but the findings need to be treated as a failure to replicate the G × E effect.

There are two other studies that are possibly relevant for G × E in relation to this general area of psychopathology. Ozkaragoz and Noble (2000) found that the D2 dopamine receptor (DRD2) had no effect on the personality traits of extraversion and neuroticism but that children with the minor alleles of DRD2 gene showed a greater extraversion score when living in an alcoholic than in an non-alcoholic home, whereas children with major alleles of the DRD2 gene showed a trend in the opposite direction. Madrid, MacMurray, Lee, Anderson, and Comings (2001) found that the DRD2 genotype showed no significant effect on alcoholism as measured by a screening questionnaire. Similarly, there was no significant main effect of stress as measured by questionnaire. On the other hand there was a significant interaction between the DRD2 genotype and stress. For a variety of reasons, noted by the authors, these findings must be regarded as preliminary and in need of replication, but they do provide possible pointers of G × E with a gene that is separate from the MAOA gene.

The findings on G × E with respect to the MAOA gene are less solid than those for the serotonin transporter gene but the rigorous checks undertaken by Caspi et al. (2002) to test the validity of the finding, plus the confirmation in Foley et al. (2004), make it likely that the G × E is both real and biologically important.

Schizophrenia spectrum disorders: quantitative findings

Environmental risk factors for schizophrenia spectrum disorders have been shown with respect to prenatal malnutrition and infections (Cannon, Dean, & Jones, 2004) and various postnatal risks (Boydell, van Os, & Murray, 2004), including heavy early use of cannabis (Arseneault, Cannon, Witton, & Murray, 2004; Henquet et al., 2005), rearing in an urban environment (Pedersen & Mortenson, 2001; van Os, Pedersen, & Mortensen, 2004), and the stresses of living in the UK or Netherlands for individuals from an African-Caribbean background (Jones & Fung, 2005). In addition, negative expressed emotion in the family has been shown to be associated with individual differences in course and it is possible it may also play a role in causation (Leff & Vaughn, 1985). In all cases, there are marked individual differences in response to these risk factors.

Twin and adoptee studies have shown that schizophrenia has a very high heritability (about 80%) but there is only about 50% concordance with monozygotic pairs. At one time it was thought that there would be genes that provide a diagnosis-specific susceptibility for schizophrenia. Although the evidence is still inconclusive, it now appears that there may be more shared liability with the genes for bipolar disorder than used to be accepted (Craddock, O'Donovan, & Owen, 2005; Murray et al., 2004). Quite possibly, there are genes that are specific to each of those and a third set of genes that are concerned with the shared liability. The last few years have been characterised by the beginnings of multiply replicated findings regarding individual susceptibility genes – with respect to association studies, linkage studies, biological plausibility, and altered gene expression in schizophrenia. Harrison and Weinberger (2005) suggested that the catechol-O-methyltransferase (COMT) is the most plausible of the susceptibility genes a priori because of its role in monoamine metabolism and because the main genetic variant being associated with schizophrenia is functional. Its candidacy is furthered by its mapping to chromosome 22q11, which has been implicated in both the meta-analyses that have been undertaken and by the fact that hemi-deletion of this region produces the velocardiofacial syndrome (VCFS), a condition associated with a major increase in the risk of schizophrenia-like psychoses. Other replicated findings concern dysbindin and neuroregulin 1, as well as several other genes.

Several studies have suggested that G × E is likely to be operating in relation to schizophrenia spectrum disorders. Carter, Schulsinger, Parnas, Cannon, and Mednick (2002) used the Copenhagen high risk project to compare the offspring of mothers with schizophrenia and the offspring of normal parents and grandparents. Genetic risk was indexed by whether or not there was schizophrenia in neither parent, one parent, or two parents. The rearing environment was indexed by institutional care and family instability. Scarcely any cases of either schizophrenia or spectrum personality disorders were found in the genetic low risk group but within the genetic high risk group there was a strong effect of the rearing environment. The implication was of a G × E interaction but there were too few cases of schizophrenia in the offspring in the genetic low risk group to provide an adequate test of G × E. Also, the environmental risk term was formed by multiplying the sum of five rearing variables by the level of genetic risk, without control for the contribution of the individual components. Accordingly, although there is a strong suggestion of a likely interaction, it is not conclusively shown.

Tienari et al. (2004) used the Finnish Adoption Study to compare the adopted-away offspring of mothers with diagnoses of schizophrenia-spectrum disorders and adopted-away offspring of biological

mothers without such diagnoses (see also Tienari, 1991, 1999). Detailed interviews in the home were used to generate measures of family relationships and communication. It was found that in the high genetic risk group there was a significant association between disordered rearing and the diagnosis of a schizophrenia spectrum disorder in the offspring, but this was not found in the low genetic risk group. A logistic regression model showed significant genotype and environment main effects, but a major effect of G × E. Thus, the adjusted odds ratio for the environment was 1.11 in the low genetic risk group but 10.0 in the high genetic risk group. The outcome being studied here concerned a somewhat broad range of schizophrenia spectrum disorders and, therefore, there must be some uncertainty on how far the findings apply to schizophrenic psychoses as such. What the findings show is that schizophrenia spectrum disorders were a consequence of genetic risk (i.e., there were very few such disorders in the control group without a genetic risk) but that, within the familial high risk group, the likelihood that disorder would develop was much higher when there were maladaptive features in the adoptive home rearing environment.

Van Os et al. (2004), using Danish Register data, found a significant interaction between urbanicity and family history. As the authors point out, family history provides only a proxy genetic risk factor and urbanicity similarly provides only a proxy environmental risk factor. Nevertheless, the pattern of findings implies G × E.

A possible G × E interaction with respect to cannabis use was suggested by the finding in a study by Henquet et al. (2005) that there was a significant interaction between schizophrenia predisposition as measured by self-reported paranoid ideation and related features and the heavy use of cannabis in relation to the onset of later psychotic symptoms. It is unlikely that cannabis represented self-medication because there was no association between predisposition and later cannabis use.

Schizophrenia spectrum disorders: molecular genetic and measured environment findings

Caspi et al. (2005) used the Dunedin Longitudinal study to investigate the possibility of G × E with respect to the COMT valine allele and heavy early use of cannabis. The reasons for focusing on the COMT gene were the same as those highlighted later by Harrison and Weinberger (2005), plus the evidence suggesting that the risk effects of cannabis may be mediated through the same dopamine pathway that is influenced by the COMT gene. The findings showed that there was no significant main effect of the genotype, that there was a main effect of adolescent cannabis exposure, and a significant interaction between genotype and adolescent cannabis use. The interaction was evident on a range of different measures of schizophrenic features. Prospective data established that the G × E antedated the onset of psychosis and carriers of the valine allele were not more likely than those carrying the met allele to use cannabis. The finding that the results applied only to early use of cannabis is consistent with the animal evidence that the effects of cannabis on brain function are restricted to the pre-adult years (Pistis et al., 2004; Schneider & Koch, 2003). The finding that the risks for schizophrenia derived only from cannabis use and not from 'hard' drugs such as heroin or cocaine implied that the risk is likely to have operated through biochemical pathways, rather than through social stressors and peer group pressures or stigma, all of which would be likely to be greater with drugs other than cannabis. It is relevant that genetic influences on substance use, abuse and dependence tend to be general, rather than specific to individual substances (Kendler, Prescott, Myers, & Neale, 2003b). The specificity of the genetic effect was investigated by replacing the COMT genotype with the MAOA and 5-HTTLPR genes that have been found to be involved in G × E with respect to depression and to antisocial behaviour. No G × E was found for these genes in relation to the schizophrenia spectrum outcomes. Similarly, replacing cannabis use with the other environmental risks previously studied (maltreatment and stressful life events), it was found that COMT did not moderate the influence of those risks on psychosis outcomes. The G × E between COMT and early cannabis use was specific to schizophrenia-spectrum outcomes apart from an extension to depression. The findings are limited by the need to rely on spectrum diagnoses (because of statistical power considerations) and, because the finding has yet to be replicated, there must be caution about the validity of the finding. Nevertheless, it is in keeping with the evidence as a whole and, as with the other two reports from the Dunedin Study, rigorous efforts were made to test for possible artefacts, all of which could be ruled out. It remains to be seen whether the G × E will be replicated by other investigators.

The diagnostic specificity of the COMT finding is called into question by the report from Thapar et al. (in press) of a significant G × E between the valine variant and low birth weight with respect to effects on conduct disorder problems in a sample of children with ADHD. The finding has yet to be replicated but it serves as a reminder that many gene effects will relate to physiological functions (in the case of COMT associated with the prefrontal cortex), rather than to psychiatric categories.

Overview of G × E

The explosion of interest in G × E across the whole of medicine has been accompanied by a diversity of reviews dealing with various conceptual and methodological considerations. Kleeberger and Peden (2005),

also Hoffjan et al. (2005), emphasised the need to examine biological pathways in their review of G × E in relation to asthma and other respiratory diseases. Talmud (2004) made the same point in relation to G × E with respect to coronary artery disease. Moffitt et al. (2005) similarly emphasised the crucial importance of investigating the biological underpinning of G × E in relation to psychopathology. As noted in the examples studied, it is both the consistency of pointers towards G × E and the biological findings that provide compelling evidence for the likely importance of G × E. McClearn (2004) underlined the value of animal models in understanding the interplay between genetic and environmental factors in their influence on complex phenotypes. The value of findings on G × E, therefore, primarily lies in their potential for understanding the causal pathways with respect to both genetic and environmental mechanisms in the origins of psychopathology.

Because of the great importance of G × E, but also the challenges in testing its validity, the greatest discussion, in recent times, has centred around the topic of research design and statistical methods (Liu, Fallin, & Kao, 2004). Thus, there has been advocacy of the advantages of a design combining both population-based controls and siblings (Andrieu & Goldstein, 2004) and family-based case–control studies (Chatterjee, Kalaylioglu, & Carroll, 2005), as well as for the use of sequential tests in matched case–control studies (van der Tweel & Schipper, 2004). In addition, there have been efforts to develop novel statistical methods for examining G × E in case–parent triad designs, with an emphasis on the need to be concerned with spurious findings resulting from genetic population admixture (Lake & Laird, 2003). The implicit assumption throughout has been that some variant of the case–control design is the preferred strategy and that the starting point should be the susceptibility genes.

By contrast, Moffitt et al. (2005, in press) argued that, although case–control designs have their place, they are not optimal for looking at biological gene–environment interactions. Because, in the present state of knowledge, the heterogeneity in response to environmental hazards constitutes the key background evidence base, it makes sense to have the environmental risk factor as the starting point. That means that one needs to have a general population epidemiological sample in order to utilise both the range of risks and the range of outcomes. Longitudinal data are important, too, because without longitudinal data it is not possible to sort out time relationships with respect to environmental hazards preceding onset of disorder (a crucial concern in testing hypotheses about environmental mediation). A further point is that the research needs to be predicated on the basis of focused hypotheses about possible biological pathways that bring together the effects of genes and environment, rather than an open-ended search for statistical interactions, which is likely to result in a huge number of false positive findings. In the future, it may be that the starting point could be genes that have been shown to affect susceptibility to environmental hazards (rather than genes that are associated with a disorder outcome), but there are very few genetic data that fulfil that need at the moment. Accordingly, at present what is needed are prospective studies of populations exposed to specific environmental risks. Ultimately, all interactions are reducible to focused main effects requiring appropriate contrast analyses (see Rutter & Pickles, 1991).

It is too early to be sure how useful the G × E approach will be for studying behavioural phenotypes. Initial enthusiasm for research into direct associations between genes and mental disorders has become tempered by increasing appreciation of the many methodological difficulties that make it difficult to replicate these studies (Insel & Collins, 2003). In view of this unhappy replication history, it is fair to ask if the G × E approach will also bust or boom. Some or all of the difficulties that explain failed replication in psychiatric genetics will also prove relevant for G × E studies. These explanations include publication bias, misclassification of outcome, phenotypic heterogeneity, allelic heterogeneity, ethnic population stratification, inadequate sample sizes, multiple testing, and low prior probabilities of association (Cardon & Palmer, 2003; Colhoun et al., 2003; Hunter 2005; Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003; Sullivan, Eaves, Kendler, & Neale, 2001; van den Oord & Sullivan, 2003).

The extremely low prior probability of a random gene's association with disorder can be increased to a higher probability that is less vulnerable to a chance result, if the G × E study is guided by a biologically plausible hypothesis involving a strong candidate gene and candidate environmental risk (Sullivan et al., 2001). Framing such hypotheses requires an evidence base of biological information about the gene and environmental risk factor. However, as yet the relevant evidence base remains sparse, thus G × E hypotheses remain circumstantial, and low prior probabilities remain a challenge to the validity of initial G × E findings. With respect to statistical tests of interaction, inconsistent findings across studies can be produced by altering scaling of measures, and different conclusions can be reached depending on the specific link function used for testing interaction (Rutter, 1983; Rutter & Pickles, 1991; Greenland & Rothman, 1998). G × E studies will also be susceptible to the other known difficulties in detecting interactions between any two factors in behavioural science (McCall, 1991; McClelland & Judd, 1993). Some G × E findings have been replicated thus far (Hunter, 2005; Moffitt et al., in press). However, the record of gene association studies teaches the wisdom of awaiting the meta-analyses.

One of the key methodological concerns (see for example Liu et al., 2004) has concerned the problem of studying G × E when there is also a gene–environment correlation. This has also been a key issue in behaviour genetic research using twin designs (Rutter & Silberg, 2002; Eaves et al., 2003). That has made it essential for all molecular genetic studies of G × E to test for whether the gene being studied correlates with the environmental risk factor being investigated. In no case has it done so. The only exceptions have been when the environmental risk factor concerns a behaviour such as smoking or binge drinking (Liu et al., 2004). As we have discussed, gene–environment correlations are indeed a reality and an important feature in understanding the ways in which genes operate, but they impinge on behaviours relevant for the selecting or shaping of environments, rather than individual differences in the environment as such.

Population admixture is much more of a problem in case–control studies than in epidemiological studies where such effects would have to be much more indirect. Nevertheless, as illustrated in the research review, it has been important to test for various possible artefactual influences. A major concern in all studies of G × E is the distortion created by errors in either measures of the genotype or measures of environmental risk (Wong, Day, Luan, & Wareham, 2004). As we have noted, high quality measurement of environmental risk factors is crucial and the same applies to genotyping (Cardon, 2003).

Conclusions

The main messages that derive from this review of gene–environment interplay in the origins of psychopathology are:

1. there are several quite different forms of interplay, each of which has rather different implications;
2. each, however, involves the basic point that the effects of genes and the effects of environments are not as separate as was once supposed;
3. the findings on epigenetic effects provide a convincing demonstration that, through influences on gene expression, environments can and, in certain circumstances, do moderate the effects of genes in crucially important ways;
4. variations in heritability according to environmental circumstances can be considerable, but focused, testable hypotheses and unambiguous comparisons are needed. As a result, this research approach has had little success so far in casting light on causal mechanisms;
5. there are several different types of gene–environment correlations (rGE) that play a substantial role in influencing environmental risk exposure but their impact is through the effects of parent and child behaviours in shaping and selecting environments;
6. gene–environment interactions (G × E) have been shown for several disorders and are likely to prove to be important in a broader range of multifactorial conditions;
7. the study and elucidation of the mechanisms involved in the different forms of gene–environment interplay should cast important light on basic causal mechanisms for psychopathology; and
8. an understanding of the complexities involved in gene–environment interplay may also help in avoiding misleading types of biological reductionism and stigma, whilst at the same time emphasising the importance of genes in all risk and protection pathways.

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