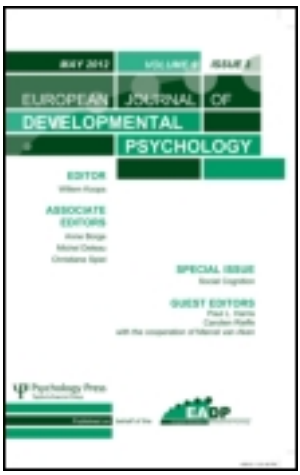

European Journal of Developmental Psychology

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/pedp20

Gene-environment interdependence

Michael Rutter [a]

[a] MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

Version of record first published: 13 Feb 2012

To cite this article: Michael Rutter (2012): Gene-environment interdependence, European Journal of Developmental Psychology, 9:4, 391-412

To link to this article: http://dx.doi.org/10.1080/17405629.2012.661174

EUROPEAN JOURNAL OF DEVELOPMENTAL PSYCHOLOGY
2012, 9 (4), 391–412

Discussion Paper

Gene–environment interdependence

Michael Rutter

MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

The modern understanding of genetic influences, of environmental effects, of mental disorder, and of heritabilities is noted. The practical utility of finding susceptibility genes with a very small effect is questioned. The empirical findings and implications of developmental perturbations, epigenetics, gene–environment correlations and interactions are then discussed. It is noted that the genes involved in gene–environment interactions may be concerned with susceptibility to all environments and not just adverse ones.

Keywords: Developmental perturbations; Epigenetics; Gene–environment correlations; Gene–environment interactions; Plasticity genes.

Over the last few decades, empirical research findings have forced several major shifts in concepts of genetic and environmental influences. Initially, behavioural genetic analyses assumed that population variance could be sub-divided into that deriving from genes and that deriving from the environment. It is now clear that such analyses result in a misleading oversimplification for six main reasons.

GENETIC CONCEPTS

First, some genetic influences mainly operate through effects on environmental risk exposure (through gene–environment correlations) or on environmental susceptibility (through gene–environment interactions). In

Correspondence should be addressed to Michael Rutter, MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, PO 80 De Crespigny Park, Denmark Hill, London SE5 8AF, UK. E-mail: camilla.azis@kcl.ac.uk

Based on an invited lecture at the 15th European Conference on Developmental Psychology, August 2011.

http://www.psypress.com/edp http://dx.doi.org/10.1080/17405629.2012.661174

both cases there is gene–environment co-action and not independent effects of each. That is, in these circumstances genes *moderate* environmental effects, rather than compete with them (Dodge & Rutter, 2011; Rutter, 2006).

Second, it had long been assumed that environments cannot influence genetic effects, but it is now known that they can, by virtue of epigenetic mechanisms (Meaney, 2010). Of course environments cannot alter gene sequences; they are present from the outset and do not change throughout life. However genes can only bring about effects if they are *expressed*. This comes about through processes that can and do change over time—as a result of the coming together of genetic, environmental, and chance (stochastic) effects. Through such epigenetic processes (which operate through developmental phase-specific and tissue-specific chemical changes), genes are in effect "switched on" and "switched off". For example there are strong genetic influences on the timing of the menarche but they do not become operative until puberty.

Third, the importance of chance effects has become better appreciated. It is a mistake to view these as mere "noise" in the system. To begin with, biological development operates on a probabilistic, not deterministic, basis. Thus, so far as the brain is concerned, there is an initial overproduction of neurons and synapses, followed by a phase of selective pruning—in effect, to "fine tune" the system—getting rid of nerve connections that serve no useful purpose and strengthening those that are needed (Nelson, 2011). This process is influenced by both genes and environment. Thus, as first shown by Hubel and Weisel (2005), and confirmed many times since, visual input is necessary for the normal development of the visual cortex. In addition, the organism is designed to adapt itself to the prevailing environmental conditions at times of sensitive periods in development (Bateson et al., 2004). As a result of the probabilistic process, minor errors are quite common—as evident, for example, in the frequency of minor (and less commonly major) congenital anomalies. These are not predictable on an individual basis, but the frequency of their occurrence is associated with known causal factors. The higher rate of Down syndrome in infants born to older mothers is the best known example, but there are many others. Probably, congenital physical anomalies, chromosomal abnormalities, and copy number variations (CNVs)—meaning submicroscopic deletions or substitutions of DNA—may be most appropriately conceptualized as varieties of developmental perturbations.

Fourth, at one time it was assumed that genes operated (via messenger RNA) only through effects on proteins, which then indirectly led on to the behavioural or phenotypic effects, through a process that remains ill-understood in almost all cases. It was, therefore, a puzzle that this accounted for so little of the effects of genes. The effects of DNA tended to be dismissed

as "junk DNA". It is now clear that this dismissal was a mistake. The process of gene expression involves not just one gene, but rather multiple DNA elements (Plomin, in press; Rutter, 2006). Moreover, many genes with important phenotypic effects do not have effects on proteins. For example, the 5HTT gene, which has been much studied in relation to G × E effects on depression, has its effects only through its role as a promoter of the action of other genes.

Fifth, it has been necessary to abandon the concept of genes "for" any individual disorder. This is partly because the effects of individual genes are so tiny, with an odds ratio rarely exceeding 1.3, and mostly far below that (Kendler, 2005). But it is also because some genetic effects with an important role in relation to disorders operate on biological pathways that are found in people without, as well as with, psychopathology (Meyer-Lindenberg & Weinberger 2006). In addition, as exemplified by the catechol-O-methyl-transferase (COMT) effect on antisocial behaviour within individuals with attention-deficit hyperactivity disorder (ADHD), but not on either antisocial behaviour or ADHD as such (Caspi et al., 2008; Thapar et al., 2005), genetic influences may operate on features within a diagnostic category, rather than on the disorder as a whole. The concept of quantitative trait loci (QTLs) that operate on continuously distributed dimensions (Plomin, in press) makes the same point. Of course geneticists have long appreciated that genes have effects on proteins rather than on disorders or behavioural traits, but the implications have become better understood.

Sixth, it is clear that some genetic influences do not follow the usual patterns. Thus, some conditions (such as the fragile X syndrome) operate through the transgenerational expansion of trinucleotide repeats (Skuse & Siegal, 2008). Others involve genomic imprinting with the result that the phenotypic effects differ according to whether the mutant gene comes through the mother or father. Quite often genetic influences operate on multiple disorders (as with schizophrenia and bipolar disorder, or autism and ADHD). Most genes, as with most environments, have pleiotropic (i.e., varied) effects. Some disorders (especially autism and schizophrenia) are associated with a markedly reduced fecundity whereas most are not. That raises the query as to why, therefore, autism and schizophrenia have not died out (Uher, 2009). The answer might lie in the role of rare, highly penetrant, pathogenic mutations, but these would not account for the high familiality of these disorders, apart from the occasional passing on to children of mutant genes that were originally de novo. Also, the main mode of operation of genes may involve protection rather than liability. This is most obvious in the field of cancer (Tobias, 2008) but almost certainly it applies more broadly. Not only have these considerations required major changes in concepts, but also new scientific findings in the years ahead are virtually certain to require yet further changes.

ENVIRONMENTAL CONCEPTS

Most of the literature considering environmental influences on psychological and psychopathological outcomes pays little attention to the meaning of the measures employed, but these are hugely important conceptual issues that require attention. First, there is the distinction between the "objective" and "effective" (or subjectively experienced) environments (Cohen et al., 2008; Singh-Manoux, Marmot, & Adler, 2005). It might seem obvious that measures of the former are to be preferred but the reverse seems to be the case. Even young infants interpret and process their experiences. The environment is actively, not passively, operative (Lewin, 1975; Radke-Yarrow, 1998), and what matters most is likely to be the perception of the individual (Brown & Harris, 1978; Clausen & Yarrow, 1955). It is clear that individuals interpret their experiences in rather different ways (Becker, 1960, 1962).

Second, a distinction needs to be made between "shared" and "non-shared" environmental effects. This distinction refers only to whether the effects make siblings more alike or not. It needs to be understood that this has no direct connection with the objective environment as such (see, e.g., Pike, McGuire, Hetherington, Reiss, & Plomin, 1996). As a consequence, the inference that a low shared effect means that family influences matter little is quite wrong.

Third, psychosocial influences extend beyond the family to include the peer group, the school, and the community, often with a complicated network of interactions between them (Bronfenbrenner, 1979; Wachs, 2000).

Fourth, as pointed out by Plomin, DeFries, and Loehlin(1977) and developed by Scarr and McCartney (1984), children both select and shape their environments (see Rutter & Rutter, 1992)—reflecting "active" and "evocative" gene–environment correlations (rGE).

CONCEPTS OF DISORDER

The notion of utterly distinct categories, which used to dominate systems of psychiatric classification, has had to be abandoned. It is not that the differences among disorders do not matter, but it is to say that the symptom overlap and the overlap among causal influences are considerable.

In keeping with the QTL concept it is clear that not only are most mental disorders multifactorial in origin, but many (perhaps most) operate dimensionally (Rutter, 2003, 2006). This is obvious in the case of depression and conduct disorder, but it is evident that the genetic effects on both autism (Folstein & Rosen-Sheidley, 2001) and schizophrenia (Kendler, Neale, & Walsh, 1995) extend well beyond the traditional diagnostic boundaries. Whether the risk operates truly across the entire general population is not known but certainly it operates beyond the traditional serious handicapping

condition concept. The multifactorial basis means an individually varying pattern of interplay among multiple genes and multiple environments. One important implication is that disorders cannot be subdivided into those due to genes (G) and those due to environments (E). Not only do most disorders involve both but also many involve a co-action between the two.

GENETIC INFLUENCES ON PSYCHOLOGICAL TRAITS AND DISORDERS

Before returning to the topic of gene–environment interplay, it is necessary to summarize some key findings on genetic influences. First, well-conducted twin, adoptee, and family studies have made it clear that there are substantial genetic influences on virtually all behaviours (Plomin, DeFries, McClearn, & McGuffin, 2008). Sometimes these are strong—as with intelligence, schizophrenia, autism, and ADHD—all of which have heritabilities exceeding 60%. In other cases, they are weaker—such as with anxiety, divorce, or religiosity—but even with these, heritability usually exceeds 20%. That there is substantial heritability for almost all behaviours is not surprising. If a behaviour has any basis in biology, there is bound to be some genetic influence. This will usually be an effect on individual differences in the degree to which people show the relevant behaviour. However, if more or less everyone has roughly the same behavioural propensity (such as the ability to develop language), there will be no heritability because there is no population variability to explain.

The second finding is that, despite these very substantial heritabilities, the effects of each individual gene that has been identified so far has been shown to be tiny even in the case of mental disorders or psychological traits that are highly heritable. This has led to the question of how to explain the apparent "hidden heritability" (Maher, 2008). The traditional answer has been that hundreds of different genes are involved, and that it is highly likely that there is huge genetic heterogeneity. This may mean, first, that the same phenotype may arise through several different genetic pathways (as, for example, the finding that autism may be associated with either the fragile X anomaly or tuberous sclerosis (TS), as well as the finding that TS is due to two different genes on chromosomes 9 and 16). Similarly, the rare genes associated with autism are also associated with intellectual impairment, ADHD, and schizophrenia (Thapar et al., 2010). Second, it may mean that within samples of people with the same phenotype the rare genes responsible in one family may differ from those responsible in other families—as has been found with copy number variations (CNVs) and autism (Pinto et al., 2010). In addition, it has been recognized that Genome-Wide Association Studies (GWAS) that have mainly been used to identify susceptibility are designed to detect common genes, but are not so efficient in picking up rare genes.

The modern answers to the "hidden heritability" paradox bring in several other considerations. Thus, the genetic effect may not map on to recognized diagnostic categories (as noted above). Genetic effects may, alternatively, be missed because they derive from influences that are pleiotropic (i.e., operate on several different phenotypes) or that depend on synergistic interactions among genes (see Flint, Greenspan, & Kendler, 2010). Also, genetic influences may operate on dimensions that extend across the general population (outside samples with a mental disorder) and, hence, may not be identified as susceptibility genes even though they are indirectly associated with psychopathology (see Meyer-Lindenberg & Weinberger, 2006). Also, the role of genetic influences may differ between the sexes. That does not mean that they operate in different ways in males and females, but rather the possibility reflects the sex differences in the frequency of particular risk factors (see Moffitt, Caspi, Rutter, & Silva, 2001).

The answer to the "hidden heritability" paradox is additionally likely to be influenced by the moderating effects of epigenetic mechanisms and by the effects of both gene–environment correlations (rGE) and interactions (G × E). Genetic influences have an indirect role on psychological outcomes as a result of effects on environmental risk *exposure* and environmental *susceptibility*.

PRACTICAL UTILITY OF SUSCEPTIBILITY GENES OF VERY SMALL EFFECT

Although many geneticists remain very positive about the practical utility of finding susceptibility genes of very small effect (see, e.g., Collins, 2010; Flint et al., 2010), a degree of scepticism is required. Sometimes the optimism is based on the hope that all (or at least most) of the many genes will be found to operate on the same biological causal pathways. If that was the case, it could lead to identification of the neural basis of the trait, but so far there is a lack of evidence that many genes do actually concern the same pathway for any particular phenotype. Sometimes the expected outcome is personalized medicine founded on the genetic differences in drug response, but if the response is multifactorially determined, that may prove problematic (Uher, 2011). Sometimes, the hope is that it will allow diagnosis to be based on causation but that is a forlorn hope in the case of multifactorial traits (Kendler, 2011). Finally, the identification of specific genes, important though that is, is of little practical value until the specific actions (via mRNA) on proteins are known *and* the means by which these chemical effects lead to the phenotype are understood. So far, that has not been achieved for any gene for a multifactorial trait or disorder.

Having made these basic points, the rest of this paper will focus only on the four main examples of gene–environment interplay, namely:

developmental perturbations; epigenetics; gene–environment correlations; and gene–environment interactions.

DEVELOPMENTAL PERTURBATIONS

The first possible mode of gene–environment interplay concerns the origin and causal role of developmental perturbations. Brain development, like that of the rest of the body, is probabilistic (Nelson, 2011). Initial neuronal overproduction is followed by neuronal pruning to correct initial errors and to enhance neuronal connections to support brain activity that seems useful. The probabilistic nature of development means that minor congenital anomalies are very common. Major anomalies, such as extra teeth or a missing muscle or a kidney with an unusual lobe structure, are less frequent but not rare. Such anomalies are not predictable on an individual basis but non-genetic influences such as a high parental age increase their frequency. Probably, on the mother's side, this arises through having old eggs (the ova are already present from before birth) but, on the father's side, it cannot arise that way because the sperm cells are created anew throughout life. Instead, it is thought that it comes about because the likelihood of anomalies rises in line with the number of cell divisions. In short, the non-genetic influence on anomalies involves chance but, in turn, the likelihood of anomalies is influenced by parental age. Do these anomalies matter for psychological development? They do not in any direct sense, but it is highly likely to be meaningful that anomalies are more common in disorders such as autism, ADHD, and schizophrenia.

Anomalies have been discussed here under the heading of developmental perturbations and it is necessary to consider what other features fall into that class. It may be suggested that chromosome anomalies and CNVs operate similarly. Some chromosome anomalies do have functional effects but many do not. Nevertheless, it is striking that they are substantially more common in individuals with autism. The same applies to CNVs. Again, some CNVs do have pathogenic causal effects on mental disorders such as autism, schizophrenia, and ADHD, but some do not. Again, however, either way, causal processes have to be considered both in terms of the origins and effects of these developmental perturbations. These constitute important research questions that have received little attention until recently.

EPIGENETICS

Epigenetics refers to the reversible regulation of gene expression, without changes in DNA sequence, mediated principally through changes in DNA methylation and chromatic structure, but also influenced by environmental features (Mill, 2011). Its importance lies in the fact that, although a person's

genes are all present from before birth and remain unchanged throughout life, the *functional consequences* of genes are entirely dependent on the genes being *expressed*. This epigenetic process is tissue specific, developmentally regulated, and highly dynamic—being influenced by genetic background, chance, and environmental features that span diet, chemicals, and rearing experiences, to mention just a few examples. Because of the environmental influences involved it may be concluded that, although the environment cannot alter the gene sequence, it can and does alter gene *effects*. Moreover, this may not only lead to phenotypic differences within monozygotic (MZ, identical) twin pairs, but also epigenetic effects on the phenotype may sometimes persist across generations.

Most of the evidence on epigenetics derives from animal models. For example, the rat studies of licking and archback nursing undertaken by Meaney, Weaver, Champagne, and colleagues, showed that this form of experience in the first week after birth (but not later) changed the chemistry involving methylation that switches genes on and off (Meaney, 2010; Weaver et al., 2005). When this involved a particular glucocorticoid gene it affected the physiology of the hypothalamic-pituitary-adrenal (HPA) response axis and, thereby, the psychological response to stress. By various forms of experimental manipulation, Meaney and colleagues showed that the effects lay in the animals' early experience and that these were mediated by the chemical changes. The consequences were long lasting and, in some instances, extended into the next generation.

Jirtle and colleagues' studies of agouti mice (see Jirtle & Skinner, 2007) focused on the effects of prenatal diet on epigenesis. When the agouti gene remains unmethylated the mouse's coat is a yellow colour and the body is obese, but when it is methylated the coat is brown. The phenotypic effects of epigenesis are obvious to the naked eye!

Genomic imprinting provides a third example—one with important disease implications in humans. Imprinted genes maintain their methylation marks throughout the normal process of reprogramming—so allowing the occurrence of different disorders according to whether a particular gene is inherited from the father or the mother. The best known human example is a genetic anomaly on the long arm of chromosome 15. If inherited through the father, the Prader–Willi syndrome is the result; if inherited through the mother the quite different condition of Angelman syndrome occurs (Skuse & Seigal, 2008).

Epigenetics is also involved in X chromosome inactivation (a process that serves to compensate for the fact that females have 2 X chromosomes—a double dose—and males just one). It has been suggested that, therefore, epigenetics could play a role in the marked sex differences in the rate of certain mental disorders such as the male excess in autism and the female excess in depression (Mill & Petronis, 2007). This has sometimes led to

claims of epigenetic causes of disorder. However, this terminology is rather misleading. Epigenetic effects only act through the genes they influence. This can be crucially important but what is possibly misleading is the implication that this can act as an independent cause, separate from genetic influences. It cannot do that. Nevertheless, there is every reason to accept both that environments can and do change the effects of genes, and that this effect could turn out to be very important in relation to normal and abnormal psychological development. Furthermore, epigenetic features could prove to be valuable biomarkers for environmental effects (Plomin, in press).

In order to determine the extent to which that is actually the case, there are methodological problems to be dealt with and substantive questions to be addressed. The main methodological challenge for human studies concerns the tissue-specificity of the epigenetic effects. For obvious reasons, brain tissues cannot be ethically studied in life, although post-mortem studies can be undertaken and have been found to be informative (McGowan et al., 2009). Otherwise, there has to be reliance on lymphocyte, or other blood element, studies. Animal studies are needed to test the extent to which the blood findings are valid indices of what is going on in the brain. In that connection, it cannot be assumed that what applies with lymphocytes will also apply to other blood elements. Similar queries apply to developmental specificity. Epigenetic findings have been found to differ within monozygotic twin pairs across the lifespan (Fraga et al., 2005).

Once these methodological issues have been dealt with successfully, key substantive questions will remain. Which environmental influences will bring about epigenetic changes? Presumably those that have a negligible psychological or physiological impact will not do so. But will the epigenetic effects of, say, abuse, neglect, and social inequality all be the same? Will the effects vary according to when the experience occurs? Will they vary according to the stage of brain development? Will they occur even in adult life? We know that major experiences in adulthood can affect brain structure (see Keating, 2011); can they also affect epigenesis?

Having answered those questions, it will still be necessary to pose other queries. Let us suppose that it will be found that serious institutional deprivation brings about epigenetic change (this is quite likely). Will epigenetic differences account for different psychological outcomes (because we know that there is huge heterogeneity in people's responses to all forms of environmental adversity)? Suppose they do. It will still be necessary to ask what brings about the proximal effect on psychological functioning. Is it the epigenetic feature? Is it the HPA effect brought about by the epigenetics, or is it some other influence? In recent times, there has been a tendency to view all adverse effects in terms of "allostatic load" (McEwen & Gianaros, 2010). But, important though that may be, we have to recognize that the HPA effects of acute and chronic stress are rather different (Gunnar & Vázquez,

2006; Loman & Gunnar, 2010). Also, are the sequelae of neglect most appropriately considered in terms of degree of stress? It is clear that both concepts and analyses must take account of multi layers without assuming that all the answers will be found in one particular layer.

GENE–ENVIRONMENT CORRELATIONS (rGE)

There are good positive reasons for expecting rGE to be quite common (Jaffee & Price, 2007; Kendler & Baker, 2007). Most of the key environmental and protective factors derive from human behaviour. This is evident, for example, in the case of marital conflict and break-up, sexual abuse, social support, and loss of a job. If human behaviour influences environmental risk exposure (which it certainly does), it follows that there will be genetic influences on risk exposure, because of the demonstrated genetic influences on such behaviour. This was shown, for example, following Ge and colleagues (Ge et al., 1996), in O'Connor and colleagues' adoption study (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). Children born to (but not reared by) mothers with drug or alcohol problems had adoptive mothers who showed more negativity towards them. More detailed analyses showed that this effect was mediated by the evocative effect of the children's disruptive behaviour on their adoptive mothers and, moreover, that this was similarly found in children *not* at genetic risk.

The existence of rGE has one very important consequence (Plomin & Bergeman, 1991). It means that even though, descriptively, a risk factor is environmental in nature, part of the *mediation* of risk is likely to be genetic and that is, indeed, what has been found. Because of this, there is an essential requirement to test for, and not just assume, environmental mediation. That is where "natural experiments" are invaluable (see Jaffee, Strait, & Odgers, 2011; Rutter 2007, in press).

Some geneticists talk as if the correlation is truly between the genes and an environment but that would imply a direct effect of G on E, which might seem (wrongly) to imply that there could be DNA in an environment. The true situation is that the rGE will be mediated by some form of *behaviour*, and that means that determining which behaviours serve to shape or select environments will be important. Equally, it will be useful to determine the extent to which genes are involved in such evocative (or active) effects. That is where genetic analyses can be highly informative.

Multivariate genetic analyses (Kendler & Prescott, 2006; Plomin et al., 2008) can identify the behaviours that mediate the genetic effect, by treating the E as a phenotype. The answers are sometimes surprising. For example, Braungart, Fulker, and Plomin (1992) found that only 23% of the genetic variance on the HOME (home environment) measure was accounted for by the child's score on the Mental Development Index (MDI) from the Bayley

scales. This ran against expectations because it might have been thought that brighter children would evoke greater parental attention to educational experiences. A further study (Saudino & Plomin, 1997) showed that task orientation (TO; including attention, persistence, goal directedness, and responsiveness) accounted for much more of the heritability of the HOME than it did the MDI. Between the MDI and the TO, all of the heritability of the HOME was accounted for.

Kendler, Jacobson, Myers, and Eaves (2007) examined comparable issues using the Virginia twin study in order to examine the mediating elements in the association between peer deviance (PD) and conduct disorder (CD). They found that rGE with respect to PD (which had an environmentally mediated effect on CD) was substantially mediated by CD (through social selection of like-minded deviant peers). Because PD was also shown to have an effect on CD, it was apparent that bidirectional processes were operative.

The next step needs to be study of the processes involved in the evocative effects of those various behaviours. Genetic strategies were useful in identifying the behaviours likely to be implicated in rGE, but study of the processes will require other research strategies. Determining the heritability of each behaviour would be of little or no interest (because it would have no policy or practice implications) but identifying the relevant individual genes (through molecular genetic research) would be informative.

GENE–ENVIRONMENT INTERACTIONS (G × E)

Although, in the past, many behavioural geneticists had tended to dismiss G × E as sufficiently unimportant and rare that is was safe to ignore it in partitioning the variance between G and E, this dismissal was based on the infrequency with which interactions had been found between anonymous genes and anonymous environments, both considered as a whole. That was not the appropriate focus both because a universally operative G × E was unlikely, and because known examples of G × E applied only to specifics (Rutter & Pickles, 1991).

There are four main positive reasons why G × E was to be expected (Rutter, 2006). First, genetically influenced differential responses to the environment constitute the mechanism that gives rise to evolutionary change. To reject G × E would mean to reject the cornerstone of evolutionary thinking. Second, to suppose that there is no G × E would require the assumption that environmental responsivity is the one biological feature that is uniquely outside of genetic influence. That seems extremely unlikely. Third, a wide range of human and other animal, naturalistic and experimental studies have shown huge heterogeneity in response to all manner of environmental features, physical and psychosocial. It is implausible that this variation involves no genetic influence. Fourth,

behavioural genetic studies have provided many pointers to likely G × E—especially in relation to depression and to antisocial behaviour (Rutter & Silberg, 2002). However, this evidence is rather circumstantial and the situation became transformed by the molecular genetic advances that allowed individual susceptibility genes to be identified and by the increasing range of "natural experiment" strategies that allowed a better testing for environmental mediation of effects.

Before turning to the empirical findings on G × E, note must be made of several key statistical issues that must be dealt with in any quality study. First, it is essential to check whether scaling variations have resulted in artefactual G × E. Second, similarly, attention must be paid to the possibility that synergistic G × G interactions could account for apparent G × E. Third, both additive and multiplicative synergistic interactions must be examined. Geneticists have tended to favour multiplicative G × E, which uses a log scale, whereas from a biological perspective, additive synergistic interactions appear more plausible (Kendler & Gardner, 2010). Fourth, attention must be paid to the possibility that rGE has given rise to a misleading impression of G × E. Fifth, proper attention must be paid to multiple tests, and findings corrected appropriately.

Risch et al. (2009) argued that it is improper to test for interactions if there is no statistical main effect. However, statisticians are divided on this issue. Both forward and backward modelling have a mixture of pluses and minuses, and dogmatic assertions that there is only one acceptable approach need to be rejected (Rutter, Thapar, & Pickles, 2009).

The Dunedin epidemiological/longitudinal studies using identified candidate genes (selected on the basis of biological findings) and measured environments were the first to produce replicated G × E in humans using these methods (Caspi et al., 2002, 2003; Caspi, Moffitt, Cannon, McClay, Murray, et al., 2005). The pattern of findings in all three cases was similar—no genetic main effect, a weak environmental main effect, and a much stronger G × E effect. Figure 1 illustrates this using maltreatment as the E, the serotonin transporter promoter gene as the G (with the so-called short allele being the one to show G × E) and the probability of a major depressive episode being the psychopathological outcome variable being studied. There have been many replications by independent research groups during the last decade (see Caspi, Hariri, Holmes, Uher, & Moffitt., 2010) and the findings seem robust—although it has to be said that the quality of the studies varies considerably.

Nevertheless, a meta-analytic review by Risch et al. (2009) claimed, not only that the Caspi et al. studies were mistaken in their claims, but also that the whole notion of G × E as applied to psychopathology was likely to be an artefact. Unfortunately, the meta-analysis was based on a biased selection of a minority of studies, was focused entirely on life events as the E, although Caspi

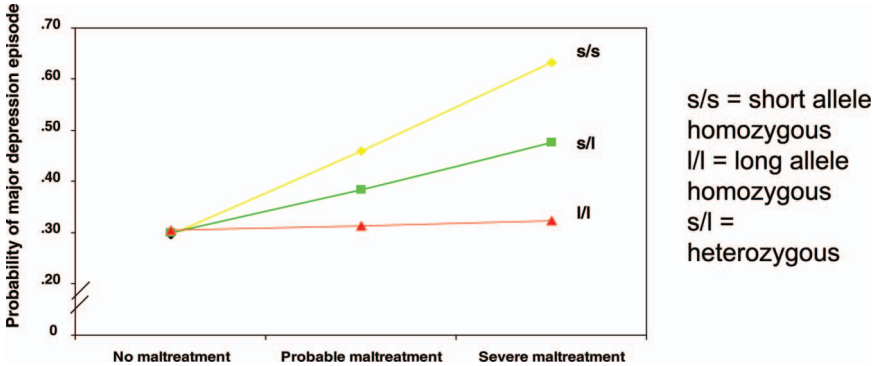

Figure 1. Effect of maltreatment in childhood on liability to depression moderated by 5-HTT gene (based, with permission, on Caspi et al., 2003).

et al.'s studies also used maltreatment as the E, was exclusively focused on a statistical, rather than a biological, concept of G × E, and totally ignored basic science, human experiments, and animal models, which taken together provide a strong case for G × E. Risch et al. (2009) also paid no attention to the numerous steps taken by Caspi et al. to test for possible scaling effects, possible G × G, possible effects of rGE, etc. There are three separate issues here. First, there is the global dismissal of G × E as a whole. That is clearly ridiculous in view of the findings from multiple research strategies (see below). Second, there is the dismissal of the Caspi et al. findings, the dismissal being seriously undermined by the flawed nature of the Risch et al. study. Third, there is the question whether the details of the G × E findings with the 5HTT gene and depression needed further scrutiny. Clearly, they did.

First, a much more extensive meta-analysis was undertaken by Karg, Burmeister, Shedden, and Sen (2011). This included 54 studies of interaction between the 5HTT gene and various forms of stress in relation to the development of depression. The analysis showed only a weak, marginally significant G × E with respect to life events (LE), but a highly significant, much stronger G × E using child maltreatment as the E. Of course, maltreatment has a much stronger risk effect than LE but, in addition, the G × E was applying to an E operating in early childhood in relation to an outcome (depression) that only became manifest in adolescence/early adult life. The implication is that the biological causal pathway operates over a long time span. Second, a study by Uher et al. (2011) on the interaction between childhood maltreatment and the serotonin transporter genotype in the Dunedin cohort showed that the G × E applied only to persistent (chronic or recurrent) depression as the outcome variable. Once again the implication is that the G × E is concerned with a continuing process affecting the liability to depression, and not provoking the onset of an episode.

So far, the evidence considered has concerned only epidemiological/longitudinal studies. One of the golden rules of science is that inferences/conclusions should be drawn from multiple research strategies, and not just one. Accordingly, attention needs to be switched next to human experimental studies using some form of intermediate phenotype (IP). IPs have to be on the same biological pathway as that leading to disorder, must involve a stress challenge that is open to manipulation, and must give rise to an immediate or non-delayed response that can be objectively measured. Ideally it is desirable to have an IP that is useful in animal models, although this cannot be a necessary requirement.

An example is provided by Hariri et al.'s (2002) study of the amygdala activation response to fearful stimuli in a normal sample, with the key comparison being between the short and long allele versions of the 5HTT genotype (see Figure 2). They found a substantially, and significantly greater, activation in those with the short allele—i.e., the same as that in the epidemiological studies. Not only does this serve as an important confirmation of the reality and meaningfulness of the G × E but, also, it showed that the interaction applied to individuals screened to be free of psychopathology, and not just those with an overt depressive disorder. The same basic strategy has been used with the MAOA gene type in relation to antisocial behaviour (Meyer-Lindenberg et al., 2006).

Evidence is also available from animal models. An example is provided by several studies from Suomi's research group using rhesus monkeys. Figure 3 illustrates Bennett et al.'s (2002) findings on the effects of the interaction between the serotonin transporter gene and the pattern of rearing (comparing peer-reared and parent-reared monkeys on central

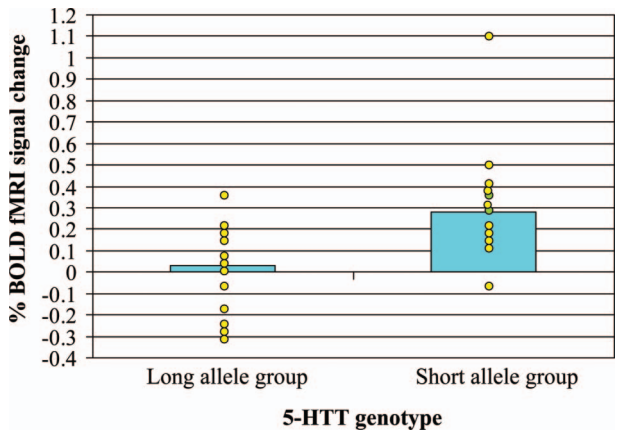

Figure 2. Effects of 5-HTT genotype on right amygdala activation in response to fearful stimuli (based, with permission, on Hariri et al., 2002).

serotonin functioning as assessed by the 5-hydroxy indole acetic acid (5-HIAA) concentrations in the cerebrospinal fluid. Earlier studies had shown the serious adverse effects of peer rearing and it seemed reasonable to regard this as a parallel to maltreatment in humans. The genes in rhesus monkeys are similar (but not identical) to those in humans and the relevant polymorphism contrast showed a G × E broadly comparable to that in humans. In summary, both human experimental studies and animal models support the reality of G × E. Just one example of each has been used as an illustration, but in both cases more extensive evidence is available. It may be concluded that multiple research strategies have confirmed the G × E finding from the epidemiological studies.

CLINICAL IMPLICATIONS OF G × E INTERDEPENDENCE

There are several important clinical implications. First, the findings on developmental perturbations highlight the need to understand why these are more common in certain mental disorders and why a high parental age might constitute a risk factor. Second, epigenetic findings have shown that experiences can alter the biology by influencing gene expression. The neurochemical mediation of this effect means that it could turn out to be appropriate to consider using medication to treat the effects of psychosocial adversities (although that remains speculative at the moment). Third, the evidence on rGE has two important implications. Its existence means that

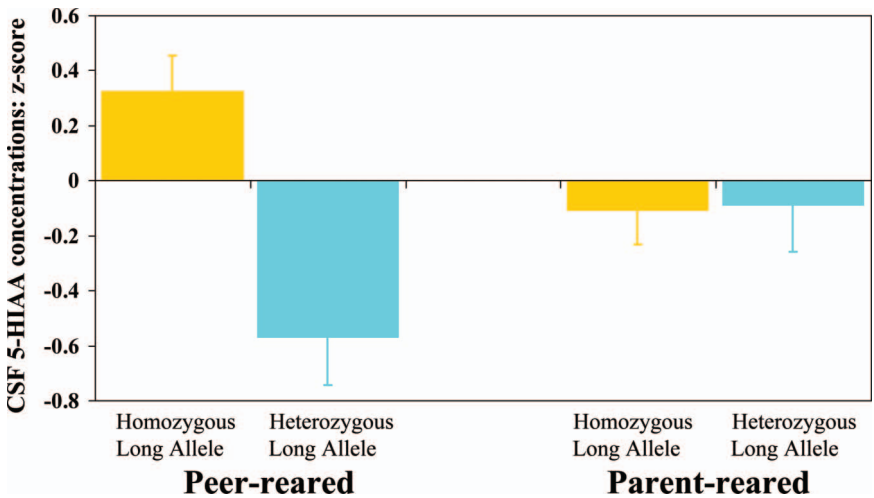

Figure 3. Effects of serotonin transporter gene and pattern of rearing on central serotonin functioning (based, with permission, on Bennett et al., 2002).

part of the mediation of the risk effects of adverse experiences may be genetic rather than environmental, making treatment strategies focusing on reducing the environmental risk less efficacious than hoped for. But, in addition, the finding that the main mediating effect of the supposed genetic influence on the environment lies in the evocative role of disruptive child behaviours, rather than any direct genetic effect, indicates the clinical importance of interventions focused on the negative evocative effects on parents (and others) of certain child behaviours.

The implications of G × E are even more important, but they require more detailed discussion because they are less self-evident. To begin with, it might be thought that the findings indicate that even such seriously adverse experiences as abuse or neglect may not matter if someone does not have the allele associated with environmental susceptibility. That would be a mistake for two different types of reason. First the evidence shows that the G × E effects are, to a considerable extent, outcome-specific. Thus, the 5HTT G × E is relevant for depression but not for antisocial behaviour. The converse applies to the MAOA gene. Doubtless, in time, other genes will be found to have effects on other outcomes. It cannot therefore be assumed that the G × E as studied so far means that abuse and neglect are harmless for some individuals because there may be ill effects on outcomes other than depression and antisocial behaviour.

The other reason is that it is probably wrong to think that the G × E means a susceptibility (or lack of it) to adverse events only. Boyce, Ellis, and Belsky have all pointed out that evolutionary considerations mean that it is likely that the susceptibility applies to most environments and not just adverse ones (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). Figure 4 illustrates the point from one of Belsky's studies (Belsky & Beaver, 2010) putting together postulated plasticity genes. The results showed that the same polymorphic variants associated with vulnerability to adverse environments were also associated with a better response to positive environments. Many questions remain regarding this suggestion but, if the hypothesis is confirmed (and the findings so far suggest it probably will be), the implication is that the G × E should be an encouragement for the likely value of therapeutic or preventive interventions, rather than the reverse (which many have wrongly assumed).

WHY DO SOME BEHAVIOURAL GENETICISTS REMAIN HOSTILE TO ANY CLAIMS ON GENE–ENVIRONMENT INTERDEPENDENCE?

Some behavioural geneticists have accepted the extensive evidence of several different forms of gene–environment co-action but some have remained hostile to the very notion. Why might this be the case? Half a dozen reasons

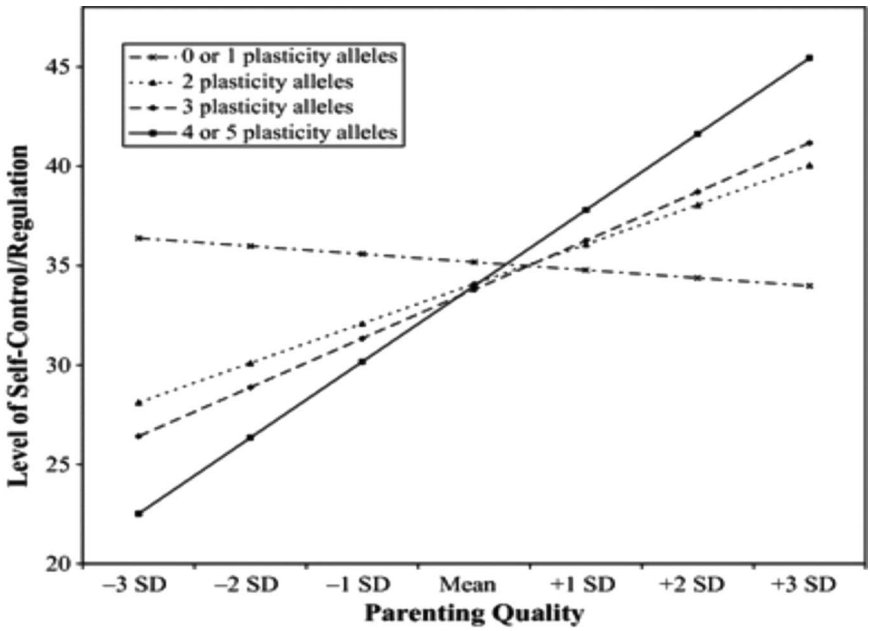

Figure 4. Interaction between cumulative genetic plasticity and parenting quality in the prediction of self-regulation for males (based, with permission, on Belsky & Beaver, 2010).

may be put forward. First, they have insisted on a focus on G × E as a statistical, rather than a biological, concept. Second, perhaps because of this, they have focused exclusively on epidemiological studies and have shown a stubborn refusal to take account of either human experimental studies or animal models. Third, they may feel defensive over their historical dismissal of G × E. Fourth, they will be aware that any adequate study of G × E co-action will require high quality E measures that have not received much attention in genetics research. Fifth, this will often mean that they would have to acquire new samples and use new research strategies. Sixth, more speculatively, they may feel resentful at the success of non-geneticists entering the genetics field.

CONCLUSIONS

Because of the likely clinical importance of gene–environment interdependence, as well as its high scientific interest, the topic should be a major growth area of research into G and into E. The existence of G × E implies that either the two (G and E) share the same biological pathway or the two pathways are closely connected in some way. That requires a focus on

biological mechanisms and it requires investigation of what genes do to proteins and how the protein products lead on to the phenotypes of interest. Similarly, it will be necessary to undertake more detailed studies of the biological effects of E—how environments in effect get ''under the skin''. The studies of G, by investigating how G has effects that operate through the environment (one feature of co-action) will comparably determine how genes get ''outside the skin''. It is obvious that no one research strategy will be adequate, that the research must not be tied to ICD or DSM (or any other) diagnostic categories, despite needing to make use of them, and that the research must involve good measures of proximal environmental influences. It is improbable that future research findings will overthrow the basic principles of gene–environment interdependence but, equally, it is certain that they will require modification of key details. The future of research into gene–environment interdependence is bright, and it may be expected that findings will alter our understanding of both normal and abnormal psychological development.

Manuscript received 7 November 2011
Manuscript accepted 19 January 2012
First published online 13 February 2012

REFERENCES

Bateson, P., Barker, D., Clutton-Brock, T., Deb, D., D'Udine, B., Foley, R. A., et al. (2004). Developmental plasticity and human health. *Nature*, *430*, 419–421.

Becker, W. C. (1960). The relationship of factors in parental ratings of self and each other to the behaviour of kindergarten children as rated by mothers, fathers and teachers. *Journal of Consulting Psychology*, *24*, 507–527.

Becker, W. C. (1962). Developmental psychology. *Annual Review of Psychology*, *13*, 1–32.

Belsky, J., & Beaver, K. M. (2011). Cumulative-genetic plasticity, parenting and adolescent self-regulation. *Journal of Child Psychology and Psychiatry*, *52*, 619–626.

Bennett, A. J., Lesch, K. P., Heils, A., Long, J. C., Lorenz, J. G., Shoaf, S. E., et al. (2002). Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Molecular Psychiatry*, *7*, 118–122.

Braungart, J. M., Fulker, D. W., & Plomin, R. (1992). Genetic mediation of the home-environment during infancy—A sibling adoption study of the home. *Developmental Psychology*, *28*, 1048–1055.

Bronfenbrenner, U. (1979). *The ecology of human development: Experiments by nature and design*. Boston, MA: Harvard University Press.

Brown, G. W., & Harris, T. O. (1978). *Social origins of depression: A study of psychiatric disorder in women*. London, UK: Tavistock.

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. (2010). Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*, *167*(5), 509–527.

Caspi, A., Langley, K., Milne, B., Moffitt, T., O'Donovan, M., Owen, M., et al. (2008). A replicated molecular genetic basis for subtyping antisocial behaviour in children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *65*, 203–210.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, *297*, 851–854.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., et al. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene–environment interaction. *Biological Psychiatry*, *57*, 1117–1127.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*, 386–389.

Clausen, J., & Yarrow, M. R. (1955). Mental illness and the family. *Journal of Social Issues*, *11*, 3–5.

Cohen, S., Alper, C. M., Doyle, W. J., Adler, N., Treanor, J. T., & Turner, R. B. (2008). Objective and subjective socioeconomic status and susceptibility to the common cold. *Health Psychology*, *28*, 268–274.

Collins, F. S. (2010). *The language of life: DNA and the revolution in personalized medicine*. New York, NY: HarperCollins.

Dodge, K. A., & Rutter, M. (2011). *Gene–environment interactions in developmental psychopathology*. New York, NY: Guilford Press.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology*, *23*, 7–28.

Flint, J., Greenspan, R. J., & Kendler, K. (2010). *How genes influence behaviour*. Oxford, UK: Oxford University Press.

Folstein, S. E., & Rosen-Sheidley, B. (2001). Genetics of autism: Complex aetiology for a heterogeneous disorder. *Nature Reviews: Genetics*, *2*, 943–955.

Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., et al. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences of the USA*, *102*(30), 10604–10609.

Ge, X., Conger, R. D., Cadoret, R. J., Neiderheiser, J. M., Yates, W., Troughton, E., et al. (1996). The developmental interface between nature and nurture: A mutual influence model of child antisocial behaviour and parenting. *Developmental Psychology*, *32*, 574–589.

Gunnar, M., & Vázquez, D. M. (2006). Stress, neurobiology and developmental psychopathology. In D. Cicchetti & D. Cohen (Eds.), *Developmental psychopathology* (Vol. 2, pp. 533–577). New York, NY: Wiley.

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*, *297*, 400–403.

Hubel, D. H., & Weisel, T. N. (2005). *Brain and visual perception*. Oxford, UK: Oxford University Press.

Jaffee, S. R., & Price, T. S. (2007). Genotype–environment correlations: A review of the evidence and implications for prevention of mental illness. *Molecular Psychiatry*, *12*, 432–442.

Jaffee, S. R., Strait, L. B., & Odgers, C. L. (2011). From correlates to causes: Can quasi-experimental studies and statistical innovations bring us closer to identifying the causes of antisocial behavior? *Psychological Bulletin* (Advance online publication. doi: 10.1037/a0026020).

Jirtle, R. L., & Skinner, M. K. (2007). Environmental epigenomics and disease susceptibility. *Nature Reviews/Genetics*, *8*, 253–262.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress and depression meta-analysis revisited: Evidence of genetic moderation. *Archives of General Psychiatry*, *68*, 444–454.

Keating, D. P. (2011). *Nature and nurture in early child development*. New York, NY: Cambridge University Press.

Kendler, K. S. (2005). "A gene for . . .": The nature of gene action in psychiatric disorders. *American Journal of Psychiatry*, *162*, 1243–1252.

Kendler, K. S. (2011). Levels of explanation in psychiatric and substance use disorders: Implications for the development of an etiologically based nosology. *Molecular Psychiatry*. (epub: June 14 2011).

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: A systematic review. *Psychological Medicine*, *37*, 615–626.

Kendler, K. S., & Gardner, C. O. (2010). Interpretation of interactions: Guide for the perplexed. *British Journal of Psychiatry*, *197*, 170–171.

Kendler, K. S., Jacobson, K., Myers, J. M., & Eaves, L. J. (2007). A genetically informative developmental study of the relationship between conduct disorder and peer deviance in males. *Psychological Medicine*, *15*, 1–15.

Kendler, K. S., Neale, M. C., & Walsh, D. (1995). Evaluating the spectrum concept of schizophrenia in the Roscommon Family Study. *American Journal of Psychiatry*, *152*, 749–754.

Kendler, K. S., & Prescott, C. A. (2006). *Genes, environment, and psychopathology: Understanding the causes of psychiatric and substance use disorders*. New York, NY: Guilford Press.

Lewin, R. (1975). Brain development and the environment. In R. Lewin (Ed.), *Child alive: New insights into the development of young children* (pp.193–206). London, UK: Maurice Temple Smith.

Loman, M. M., & Gunnar, M. R. (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience & Biobehavioral Reviews*, *34*, 867–876.

Maher, B. (2008). The case of the missing heritability. *Nature*, *456*, 18–21.

McEwen, B., & Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: Links to socioeconomic status, health and disease. *Annals of the New York Academy of Sciences*, *1186*, 190–222.

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., et al. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associated with childhood abuse. *Nature Neuroscience*, *12*(3), 342–348.

Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development*, *81*(1), 41–79.

Meyer-Lindenberg, A., Buckholtz, J. W., Kolachana, B., Hariri, A. R., Pezawas, L., Blasi, G., et al. (2006). Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences of the USA*, *103*, 6269–6274.

Meyer-Lindenberg, A., & Weinberger, D. R. (2006). Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Reviews Neuroscience*, *7*, 818–827.

Mill, J. (2011). Epigenetic effects on gene function and their role in mediating gene–environment interactions. In K. S. Kendler, S. R. Jaffee, & D. Romer (Eds.), *The dynamic genome and mental health: The role of genes and environments in youth development* (pp. 145–171). New York: Oxford University Press.

Mill, J., & Petronis, A. (2007). Molecular studies of major depressive disorder: The epigenetic perspective. *Molecular Psychiatry*, *12*, 799–814.

Moffitt, T. E., Caspi, A., Rutter, M., & Silva, P. A. (2001). *Sex differences in antisocial behaviour: Conduct disorder, delinquency, and violence in the Dunedin longitudinal study*. Cambridge, UK: Cambridge University Press.

Nelson, C. A. (2011). Neural development and lifelong plasticity. In D. P. Keating (Ed.), *Nature and nurture in early child development* (pp. 45–69). New York, NY: Cambridge University press.

O'Connor, T. G., Deater-Deckard, K., Fulker, D., Rutter, M., & Plomin, R. (1998). Genotype–environment correlations in late childhood and early adolescence: Antisocial behavioural problems and coercive parenting. *Developmental Psychology*, *334*, 970–981.

Pike, A., McGuire, S., Hetherington, E. M., Reiss, D., & Plomin, R. (1996). Family environment and adolescent depression and antisocial behavior: A multivariate genetic analysis. *Developmental Psychology*, *32*, 590–603.

Pinto, D., Pagnamenta, A. T., Klei, L., Anney, R., Merico, D., Regan, R., et al. (2010). Functional impact of global rare copy number variations in autism spectrum disorders. *Nature*, *466*, 368–370.

Plomin, R. (in press). Child development and molecular genetics: 13 years later. *Child Development*.

Plomin, R., & Bergeman, C. S. (1991). The nature of nurture: Genetic influence on "environmental" measures. *Behavior and Brain Sciences*, *14*, 373–427.

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype–environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin*, *84*, 309–322.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2008). *Behavioral genetics*. New York, NY: Worth Publishers.

Radke-Yarrow, M. (1998). *Children of depressed mothers: From early childhood to maturity*. Cambridge, UK: Cambridge University Press.

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., et al. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *Journal of the American Medical Association*, *301*, 2462–2471.

Rutter, M. (2003). Categories, dimensions, and the mental health of children and adolescents. *Annals of the New York Academy of Sciences*, *1008*, 11–21.

Rutter, M. (2006). *Genes and behaviour: Nature–nurture interplay explained*. Oxford, UK: Blackwell Scientific.

Rutter, M. (2007). Proceeding from observed correlation to causal inference: The use of natural experiments. *Perspectives in Psychological Science*, *2*, 377–395.

Rutter, M. (in press). Resilience: Clinical implications. *Journal of Child Psychiatry and Psychology*.

Rutter, M., & Pickles, A. (1991). Person–environment interactions: Concepts, mechanisms, and implications for data analysis. In T. D. Wachs & R. Plomin (Eds.), *Conceptualization and measurement of organism–environment interaction* (pp. 105–141). Washington, DC: American Psychological Association.

Rutter, M., & Rutter, M. (1992). *Developing minds: Challenge and continuity across the life span*. New York, NY: Basic Books.

Rutter, M., & Silberg, J. (2002). Gene–environment interplay in relation to emotional and behavioral disturbance. *Annual Review of Psychology*, *53*, 463–490.

Rutter, M., Thapar, A., & Pickles, A. (2009). Gene–environment interactions: Biologically valid pathway or artefact? *Archives of General Psychiatry*, *66*, 1287–1289.

Saudino, K. J., & Plomin, R. (1997). Cognitive and temperamental mediators of genetic contributions to the home environment during infancy. *Merrill-Palmer Quarterly Journal of Developmental Psychology*, *43*, 1–23.

Scarr, S., & McCartney, K. (1984). How people make their own environments: A theory of genotype → environment effects. *Child Development*, *54*, 424–435.

Singh-Manoux, A., Marmot, M. G., & Adler, N. E. (2005). Does subjective social status predict health and change in health status better than objective status? *Psychosomatic Medicine*, *67*, 855–861.

Skuse, D. H., & Siegal, A. (2008). Behavioral phenotypes and chromosomal disorders. In D. Bishop et al. (Eds.), *Rutter's child and adolescent psychiatry* (5th ed., pp. 3–17). Oxford, UK: Blackwell.

Thapar, A., Langley, K., Fowler, T., Rice, F., Turic, D., Whittinger, N., et al., (2005). Catechol-O-methyltransferase gene variant and birth weight predict early onset antisocial behavior in children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *62*, 1275–1278.

Thapar, A., Williams, N. M., Zaharieva, I., Martin, A., Langley, K., Mantripragada, K., et al. (2010). Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: A genome-wide analysis. *The Lancet*, *376*, 1401–1408.

Tobias, E. S. (2008). The molecular biology of cancer. In D. L. Rimoin, J. M. Connor, R. E. Pyeritz, & B. R. Korf (Eds.), *Emery and Rimoin's principles and practice of medical genetics* (5th ed., Vol. 1, pp. 389–442). London, UK: Churchill Livingstone.

Uher, R. (2009). The role of genetic variation in the causation of mental illness: An evolution-informed framework. *Molecular Psychiatry*, *14*, 1072–1082.

Uher, R. (2011). Genes, environment, and individual differences in responding to treatment for depression. *Harvard Review of Psychiatry*, *19*, 109–124.

Uher, R., Caspi, A., Houts, R., Sugden, K., Williams, B., Poulton, R., et al. (2011). Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: Replications and implications for resolving inconsistent results. *Journal of Affective Disorders*, *35*, 56–65.

Wachs, T. D. (2000). *Necessary but not sufficient: The respective roles of single and multiple influences on individual development*. Washington, DC: American Psychological Association.

Weaver, I. C., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., et al. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. *Journal of Neuroscience*, *25*, 11045–11054.