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The contribution of gene–environment interaction to psychopathology

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Abstract

The study of gene–environment interaction (G × E) constitutes an area of significant social and clinical significance. Different types of research study designs are being used to investigate the contribution of G × E to psychopathology, although the term G × E has also been used and interpreted in different ways. Despite mixed evidence that G × E contributes to psychopathology, some promising and consistent findings are emerging. Evidence is reviewed in relation to depression, antisocial behavior, schizophrenia, and attention-deficit/hyperactivity disorder. Although findings from various research designs have different meaning, interestingly much of the evidence with regard to the contribution of G × E that has arisen from twin and adoption studies has been for antisocial behavior and depression. It is for these same forms of psychopathology that molecular genetic evidence of G × E has also been most convincing. Finally, current and anticipated methodological challenges and implications for future research in this area are considered.

In the last two decades there has been a rapidly expanding research literature showing that the origins and developmental course of different types of psychopathology are influenced by genes and environmental factors that work together in complex ways (Rutter, 2006, 2007). Although it has been known for some time that both genetic and environmental risk factors contribute to the development of psychopathology, regardless of whether considered as categorically defined psychiatric diagnoses or as continuously distributed trait measures, it is only relatively recently that attention has turned to investigating how genes and environmental factors work together to account for variation in psychopathology across the life course (Plomin, DeFries, Craig, & McGuffin, 2003). The present article focuses on a review of research relating to the investigation of gene–environment interaction (G × E) in some of the most common forms of psychopathology.

We use the term interplay to encompass the processes by which genes and environmental hazards or risk factors work together in influencing traits and disorders (phenotypes). Although the term G × E is now widely used in the fields of developmental psychopathology, psychiatry, and medicine, it can be used to describe very different scenarios. At a conceptual level for the purposes of this article we consider G × E to refer to the situation where genetic factors influence individual sensitivity or response to environmental adversity or context. The practicalities of research design mean that the presence of G × E is deduced statistically. This does not, however, necessarily mean that interaction also occurs biologically, although clearly that is the hope. To show biological interaction, other sorts of experiments and designs will be needed. Finally, even where the presence of G × E is deduced statistically, this, too, can mean one of several different things depending on the type of research design used.

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Given there is now overwhelming evidence that genes and environmental factors both contribute to psychopathology and common diseases and disorder and that their effects are intertwined, there is an increasing appreciation that any research aimed at identifying risk and protective factors and etiological pathways needs to consider the contribution of both. Thus, increasingly the investigation of gene–environment interplay has become recognized to be an important research area in psychiatry, psychology, clinical epidemiology, and developmental psychopathology (Institute of Medicine, 2006; Rutter, 2006). There has also been an appreciation of its importance for common medical disorders such as asthma (Dizier et al., 2007; Ramadas et al., 2007) and heart disease (Talmud et al., 2007). There is also recognition that the contribution of environmental risk factors is relevant to mainstream genetic studies that are purely aimed at identifying susceptibility genes for psychiatric disorder and common clinical conditions. Here, the contribution of environmental factors is becoming incorporated into traditional molecular genetic study designs to aid identification of susceptibility genes (Chatterjee, Kalaylioglu, Moslehi, Peters, & Wacholder, 2006). Finally, the implications of G × E have also become more compelling, as findings are beginning to be replicated.

Despite this enthusiasm, there are many issues that also require critical consideration. There are a variety of strengths and weaknesses of different types of methodology, research designs, and analytic methods (Moffitt, Caspi, & Rutter, 2005; Rutter, Moffitt, & Caspi, 2006). It is not straightforward evaluating the strength of evidence and in establishing that the overall conclusions are in favor of G × E. Once G × E is detected, it will be even more challenging to establish the mechanisms that underlie causal effects on psychopathology.

One issue that is of particular relevance to developmental psychopathology is the phenomenon whereby the effects of genes and environmental factors are not independent. Exposure to environmental risk is not random and environmental factors can also mediate genetic risks (Rutter, Pickles, Murray, & Eaves, 2001). For example, a genetic risk variant or, more broadly, overall genetic liability could potentially exert its risk effects on psychopathology by influencing an individual's exposure to an environmental hazard.

This interrelationship of genes and environment is known as gene–environment correlation (Plomin et al., 2003). There are now good examples that gene–environment correlation is important in developmental psychopathology (Jaffee, & Price, 2007). It does not necessarily mean that the environmental risk factor has no true risk effects, but it does raise the possibility that the association between the risk factor and psychopathology arises because of shared genetic factors that influence both the environment and the outcome (Rutter et al., 2001). Genetically sensitive research designs such as twin and adoption study designs and variants of such methods have been used to investigate gene–environment correlation and to test whether associations between measured environmental factors and psychopathology are environmentally mediated (Rutter, 2006; Rutter et al., 2001).

For example, twin studies have shown that genetic influences on adolescent depression appear to be partly mediated through exposure to life events (Eaves, Silberg, & Erklani, 2003; Rice, Harold, & Thapar, 2003; Silberg et al., 1999) whereas adoption studies of childhood antisocial behavior suggest that genetic influences on child antisocial behavior appear to be partly mediated by the risk effects of negative parenting evoked by an adopted child who is at higher genetic risk (Ge et al., 1996; O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). Findings from these adoption studies of antisocial behavior (Ge et al., 1996; O'Connor et al., 1998) provide a good example of the conceptual overlap between gene–environment correlation and person–environment correlation (Bell, 1968).

Taking the same issue from another perspective, twin and adoption studies have also been used to test whether environmental risk factors have true environmentally mediated risk effects (Rutter et al., 2001). Such designs have, for example, shown that maltreatment has environmentally mediated risk effects on child antisocial behavior (Jaffee et al., 2004). Other studies indicate genetic mediation of environmental

effects; for example, the adoption study suggesting both genetic and environmental mediation of negative parenting on childhood antisocial behavior (O'Connor et al., 1998).

The presence of gene–environment correlation is also of importance in that such effects may lead to the detection of G × E effects where none exist. Given that many important environmental risk factors for psychopathology will show gene–environment correlation, it is important to consider and test the possibility of confounding effects of gene–environment correlation and G × E. These methodological considerations have been previously highlighted and discussed in detail (Jaffee & Price, 2007; Moffitt, Caspi, & Rutter, 2006; Moffitt et al., 2005; Rutter, 2007; Rutter et al., 2006). Issues relating to gene–environment correlation, therefore, will not be covered further in this paper but the interested reader is referred to several useful sources (Jaffee & Price, 2007; Rutter, 2006).

In this article we review G × E findings for four psychiatric disorders/forms of psychopathology; depression, antisocial behavior, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD). Findings will be considered according to the different type of study design as the interpretation of results differs according to the research design employed.

G × E in Which Genetic Influences Are Inferred Using Traditional Twin, Adoption, and Other Family-Based Designs

Traditional genetic designs, notably twin and adoption studies, are based on statistically inferring genetic liability to a given condition by examining the phenotypic similarity and dissimilarity of individuals who differ in their degree of genetic relatedness. These designs infer overall genetic liability that will include the effects of *all* different genetic risk factors. However, the methods used to test for evidence of G × E in twin studies are not the same. Detailed overviews of these research designs and their strengths and drawbacks are available elsewhere (Moffitt et al., 2005; Rutter et al., 2006).

A frequently used method of testing for G × E involves testing whether the proportion of variance attributable to genetic (and environmental) effects for a given phenotype, for example antisocial behavior, is moderated by environmental risk exposure (Purcell, 2002). Essentially, this method involves testing for heterogeneity in terms of the contribution of genetic (and environmental) variance to a phenotype for a given population where the population is defined according to exposure to environmental risk or level of environmental risk. Although the findings of this type of design can be difficult to interpret in terms of what they might mean at an individual level (Rutter et al., 2006), they are able to essentially highlight whether there appears to be etiological heterogeneity that varies depending on a given environmental risk factor.

An alternative method, that is more intuitively meaningful, involves testing whether the risk of disorder is increased where individuals are at higher inferred genetic risk and are exposed to the environmental risk, than among those at lower genetic risk. However, a drawback to this method lies in accurately defining genetic risk. For example, for some disorders such as depression, a twin may not have passed through the age of risk, and thus inferring genetic risk may be problematic. There have now been a number of different published studies where genetic risk is inferred and the contribution of G × E to depression and antisocial behavior is examined. There has been much less of this type of work on ADHD and schizophrenia using such designs.

Depression

There have been several twin studies that have investigated the contribution of G × E to depression using the variance components method. These have primarily focused on family adversity, specifically, family conflict and negative life events. However, findings have been mixed. In one recent twin study of adolescent depression (Rice, Harold, Shelton, & Thapar, 2006), genetic variance was lower in the presence of higher levels of family conflict and became higher with declining levels of conflict. That is, there appeared to be significant effects of Genetic Variance × Family Conflict "interaction." However, the results of a more recent study suggest that parental warmth and

hostility do not appear to moderate (interact with) genetic variance for depression (Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007). When life events are considered as the index of family adversity, G × E findings for life events and depression have been much more consistent. The first twin study of life events and adult depression (Kendler et al., 1995) showed that those at higher genetic risk of depression, inferred by virtue of having a genetically identical monozygous co-twin with depression, had a greatly increased risk of depression when exposed to life events. That is, the impact of life events was higher for those who were also at higher genetically liability of developing depression. Similar findings were subsequently found for adolescent girls also using a twin study design (Silberg, Rutter, Neale, & Eaves, 2001). Finally, there has been some evidence suggesting evidence of interaction between lower birth weight and genetic liability in increasing symptom levels of depression in adolescents (Rice et al., 2006), but this finding has yet to be replicated.

Antisocial behavior

Replicated findings have come from a variety of research designs that show G × E contributes to antisocial behavior. Many of these studies have highlighted the importance of negative early parenting and adverse family environment. In a twin study of children, maltreatment was found to have a greater adverse impact in those at increased genetic risk of antisocial behavior (Jaffee et al., 2005). In another twin study of childhood antisocial behavior, but one employing the variance components method, evidence of etiological heterogeneity in terms of differences in genetic and environmental variance according to the level of family dysfunction was provided (Button, Scourfield, Martin, Purcell, & McGuffin, 2005). A more recent twin study also found evidence of increased genetic variance with increased socioeconomic status and increased shared environment variance for twins from families of lower socioeconomic status (Tuvblad, Grann, & Lichtenstein, 2006). Most recently, findings from the Nonshared Environment in Adolescent Development Study (Feinberg et al., 2007) showed that genetic and environmental variance for antisocial behavior changed depending on levels of parent hostility and warmth to the child. However here, genetic variance was greater for children from more negative family backgrounds (lower levels of warmth, higher levels of hostility); that is, the findings are in an opposite direction to those of Button and colleagues (2006) and Tuvblad et al. (2007), although adversity in the form of family dysfunction, lower socioeconomic status, and quality of parent–child relationship cannot be equated.

Adoption study findings converge with those from twin studies in showing that early adverse environments have a greater negative impact on genetically "higher risk" children. Such studies have shown that children with antisocial biological parents who have been adopted away show higher rates of antisocial behavior when reared in a family where there is adversity than children exposed to adversity but who do not have antisocial biological parents and those who are at higher genetic risk but who are not exposed to adversity in the adoptive home (Cadoret, Cain, & Crowe, 1983; Rutter, Giller, & Hagell, 1998). Thus, for antisocial behavior there is reasonably consistent evidence of interaction between genetic liability and early family adversity.

Schizophrenia

Although schizophrenia is recognized as one of the more heritable of the psychiatric disorders, and there is evidence to suggest that prenatal factors, for example, poor nutrition in utero (St. Clair et al., 2005; Susser & Lin, 1992), psychosocial adversity, and early cannabis use (Henquet, Murray, Linszen, & van Oz, 2005; Rutter et al., 2001) are associated with the disorder, there has been less research in the form of investigating G × E using traditional genetic designs. However, two adoption studies suggest that genetic liability to schizophrenia spectrum disorders interacts with adverse rearing in increasing the risk for schizophrenia spectrum disorders in adopted away offspring (Tienari et al., 2004; Wahlberg et al., 1997). There have also been studies suggesting that familial risk (not the same as genetic) modifies the association between exposure to an urban

environment and schizophrenia (Krabbendam & van Os, 2005).

ADHD

Despite the strong interest in the genetic etiology of ADHD, with numerous published twin studies (Faraone et al., 2005; Thapar, Holmes, Poulton, & Harrington, 1999; Thapar, Langley, Asherson, & Gill, 2007), there has been remarkably little work thus far investigating the contribution of G × E to ADHD using traditional research designs. This is also surprising, given that clinical and epidemiological studies have suggested that environmental factors are associated with ADHD. The most consistent evidence of association shown using meta-analyses or pooled analyses has been observed between lower birth weight (Bhutta, Cleves, Casey, Cradock, & Anand, 2002), maternal smoking in pregnancy (Langley, Rice, van den Bree, & Thapar, 2005), and ADHD. Twin studies have suggested that the association between lower birth weight and ADHD appears to be mediated environmentally (Hultman et al., 2007; Lehn et al., 2007). In contrast, the association between alcohol use in pregnancy and ADHD (and here evidence for association is equivocal) appears to be genetically mediated (Knopik et al., 2006). A difficulty with examining family adversity is that there is evidence from longitudinal and treatment studies that, for ADHD, adversity arises in part from a person–environment effect that is influenced by the child's ADHD symptoms (Barkley, Karlsson, Pollard, & Murphy, 1985; Schachar, Taylor, Wieselberg, Thorley, & Rutter, 1987). However, investigations of G × E for ADHD using traditional designs do not appear to have been published. One possibility is negative publication bias; where G × E is not found the negative results are not published.

G × E Involving Genetic Risk Measured in the Laboratory

Molecular genetic studies allow a different type of investigation of G × E. The findings from this type of study are currently generating enormous interest. Initial findings inevitably have to be met with caution but replications for some, but not all, findings are emerging. Probably the most convincing set of findings is that traditional twin and adoption studies have most frequently implicated G × E as contributing to the phenotype for antisocial behavior. For the purpose of understanding recent findings, a basic understanding of molecular genetics is required, although the interested reader is directed elsewhere (Rutter, 2006).

Genetic risk as measured in the laboratory can have several different meanings. An individual's genome is made up of genes that code for proteins and noncoding regions. The latter are increasingly being recognized as playing a more important role than previously thought (Thapar, & Rutter, 2007). Molecular genetic studies aimed at identifying susceptibility genes (that is testing main gene effects) for disorder essentially involve laboratory characterization of sites of the genome that show genetic variation in their DNA sequence in samples of cases and controls (or variants of this design) or in families with multiply affected members. The methods by which genetic variation can be assayed have greatly evolved in efficiency over time (Thapar & Rutter, 2007), but the details are beyond the scope of this review.

Sites showing sequence variation between individuals are often described as "polymorphisms" and "mutations." These terms have broad and strict definitions, but for our purposes, we use the terms genetic variant or DNA marker to describe sites of sequence variation. The sequences at a marker are known as alleles. Because chromosomes that carry genetic material come in pairs (with the exception of gender chromosomes), an individual has two alleles. This combination of alleles is known as a genotype. Thus, a person with one chromosome carrying a sequence corresponding to an allele arbitrarily designated "1" and the other chromosome carrying an allele arbitrarily designated "2" would have a genotype of 12. The process of characterizing an individual's alleles at each marker is known as genotyping.

Although there is now sufficient genetic variation identified to provide dense coverage of the human genome (Altshuler & Clark, 2005; Couzin & Kaiser, 2007), it is important to recognize that most molecular genetic variation (including markers tested in genetic studies) does not necessarily alter gene function. However, if a variant is located close to another variant that does alter function, the sequence at the first variant site may predict that at the

functional site. As a consequence, the first variant may be useful for identifying genetic associations caused by the functional site. This process is called indirect association or association because of linkage disequilibrium (LD).

Investigation of G × E

Here, we are able to test whether the effects (direct or indirect) of an individual genetic marker or set of markers that is genotyped in the laboratory vary according to whether or not an individual is exposed to a specific environmental factor. Until now, published G × E studies have focused on DNA markers that have been selected on the basis of being within a specific gene, but that does not have to be the case.

The presence of G × E could mean that specific genetic variants may not necessarily carry risk effects on their own (i.e., main effects) and will only be associated with psychopathology when the individual carrying the variant or variants is also exposed to a specific environmental context. Thus, where G × E occurs, epidemiological and genetic studies that set out to identify causal genetic risk factors may show inconsistent findings because of sample differences in environmental exposure.

Finally, it is important to be aware that environmental factors interact with genes at a molecular and biological level (Rutter, 2006, 2007). Genes code for amino acids, the building blocks of proteins (Rutter, 2006). This process of producing amino acids is itself complicated and influenced by environmental factors. The pathways that lead from protein to the observed characteristics or disorder (phenotype) are also, unsurprisingly, complex. Thus, "environment" can impact on many different points of the complex pathways that lead from gene to "gene products" and eventually psychopathology. Here we focus on observable phenotypic manifestations of G × E.

In summary, therefore, traditional and molecular genetic methods for examining G × E are different. The first focuses on overall genetic liability that is inferred and includes the effects of all inherited risk; the second generally focuses on a single measured genetic factor as a susceptibility marker for psychopathology. Importantly, it must be recognized that results driven from studies that focus on G × E will typically vary not only as a function of the specific methodology employed but also because of the specific genetic and environmental ingredients considered in any single analysis.

Which Gene and What Type of Environment?

Testing for G × E using candidate genes thought to be involved in the disorder

To date, published studies of G × E have all focused on functional candidate genes. These are genes that are selected on the basis of assumption that they may be involved in that form of psychopathology. There are, however, a few problems with respect to this. First, one major motivation for undertaking genetic studies is to identify novel, previously unconsidered biological pathways that may be involved in a given psychiatric disorder. Second, as the pathophysiology of these conditions is not known, it is difficult to pick candidate genes in the way that is possible for diseases such as diabetes. Third, even where a candidate gene is selected, it is no straightforward task selecting variants that affect function of that gene. Previously it was thought that functional variants should be in coding regions of the gene, but now it is known that this is far too restrictive, and that variants that affect gene function can even lie outside the gene. Fourth and finally, where evidence of interaction between a marker allele and environmental factors has been found, it can be difficult to know whether that allele has risk effects or whether it is the other allele/alleles for that marker that is exerting protective effects.

Testing for G × E across the whole genome

The focus of whole genome studies is to undertake a search for genetic risk variants across all the genome rather than within a specific gene. In recent years, because of laboratory advances and reduced costs of genotyping very large numbers of genetic markers that capture individual genetic variation has become possible and more detailed investigation of the genome has become feasible. Until recently,

for complex disorders such as diabetes, schizophrenia, and autism, whole genome searches were undertaken by collecting families with multiply affected individuals and undertaking linkage studies. This involves testing multiple markers across the genome and investigating whether affected relatives share more alleles in common than expected (McGuffin et al., 2002). Linkage studies allow the identification of regions of the genome that might be involved in the disease etiology. These regions harbor many genes, and the task of undertaking fine mapping studies to find the risk variant or variants is onerous. That is, even where linkage findings are replicated, it is not straightforward to identify causal genetic risk variants. Tests of G × E can be included in such designs. Although here the situation is different from that of testing for G × E with a single gene variant, in that it essentially involves testing whether a linkage signal varies depending on exposure to a specific environmental risk factor. For example, in a recent study using this approach, evidence of G × E with smoking was found in a whole genome study of asthma (Dizier et al., 2007).

In some instances G × E could increase a linkage signal and the power to detect a genetic effect or could indicate that the environmental risk factor is interacting with a susceptibility locus (Schmidt, Qin, Schmidt, Martin, & Hauser, 2007). However, this does not necessarily mean that including environmental risk factors in the analysis will always be beneficial. The effect of some genes will not be contingent on environmental risk exposure.

Relatively recently, more detailed examination of the genome using hundreds of thousands of markers based on samples of thousands of affected cases and controls rather than multiply affected families has become possible (Couzin & Kaiser, 2007). Such whole genome association studies are yielding new successes for common disease conditions such as prostate cancer and diabetes (Couzin & Kasier, 2007; Diabetes Genetics Initiative of Broad Institute of Harvard and MIT et al., 2007; Haiman et al., 2007). As a result of these developments new analytic methods have been devised to take into account the effect of multiple genetic variants (Chatterjee et al., 2006) and that exploits G × E to increase statistical power (Kraft, Yen, Stram, Morrison, & Gauderman, 2007). However, the challenges in dealing with multiple testing in such whole genome studies where G × E is tested are considerable.

Selecting the environmental factor

This also is not straightforward. The environmental risk factor needs to be reliably measured and defined a priori. For example, considering family influences as a factor that may interact with genetic liability depends not only on the specific genetic factors at play but also the operationalization of the family factors considered. Disparity in findings may be as much a function of different approaches to estimating G × E interplay as they are a function of substantive differences in the specific impacts of low parental warmth and high parental hostility compared to general family conflict or negative life events, for example.

Ideally there should be evidence that the chosen environmental factor has causal risk effects, and in the case, where a specific gene is selected there needs to be a biological hypothesis for testing interaction (Moffitt et al., 2005). Evidence from animal studies has shown particular utility in relation to this latter requirement. For example, when testing G × E for variants in the serotonin transporter (*5-HTT*) and monoamine oxidase A (*MAOA*) genes, animal study findings have implicated that these genes or at least the proteins that they code for may be implicated in the pathophysiology of depression and antisocial behavior respectively (Rutter et al., 2006). However, the selection of environmental risk factor is not straightforward for whole genome studies as different environmental risk factors will be relevant for different genetic risk variants and different genomic regions.

Environmental risk factors impact on organisms and will interact with genes, gene products, and genetically influenced pathways at a biological level. Thus, it could be argued that from a biological perspective the exact nature of the risk factor may not be important; rather, its effect on biological mechanisms. Different risk factors may show evidence of interaction with the same gene variant for the same form of psychopathology because they impact on the same pathway. This means it could

be argued that composite measures of "adversity" or stress may be preferable or indeed measures that index the *effects* of environment on the organism; for example, biological indices of stress or groups of toxins that are metabolized by the same biological pathways. However, for clinical, intervention and risk reduction purposes, it is undoubtedly helpful to have knowledge on what the specific environmental risk factors are rather than having general measures of "stressors" or "toxin." Thus far, different research groups have adopted different approaches. Some studies have investigated single environmental risk factors such as life events; other have used composite measures of adversity. Despite these challenges, there have been some important findings that have been now widely replicated highlighting the point that some of these obstacles are surmountable.

Depression

Given twin study findings have suggested this as an important area, it is perhaps unsurprising that a considerable amount of research effort has focused on testing for G × E for life events and depression. Interest in a specific variant in the *5-HTT* gene, the linked promoter region (*5-HTTLPR*), had initially been driven by animal studies that suggested interaction of *5-HTTLPR* and adversity in affecting stress responsivity and related outcomes (Suomi, 2006).

Findings from the Dunedin longitudinal study (Caspi et al., 2002) showed initial evidence of interaction between a functional genetic variant in the serotonin transporter gene and life events. The variant affects how much serotonin transporter protein is produced, a protein involved in reuptake of serotonin from the synapse. Specifically individuals with the short allelic form of this variant showed an increased risk of depression compared to those carrying the long allele but only when exposed to adverse life events. Thus, here there was no evidence of a main genetic effect for this variant. It is interest that significant G × E interaction for depression was also detected when examining another environmental stressor: maltreatment. The finding of G × E between this 5-HTT variant and life events has now been reported in numerous studies across the lifespan from childhood and adolescence (Eley et al., 2004; Kaufman et al., 2006) to adult life (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Scheid et al., 2007; Vergne, & Nemeroff, 2006; Zammit, & Owen, 2006) and also in a different ethnic group (Kim et al., 2007). There have been some nonreplications also (Zammit & Owen, 2005), but these have now been greatly superseded by the number of replicated findings. A meta-analysis is ideally warranted, although all the studies have used somewhat different designs in terms of measurement of life events, definition of depression, or a related outcome, and even some differences with regard to defining the DNA sequence conferring risk (Zalsman et al., 2006). Thus, although findings have been mixed, generally they have been in favor of evidence for G × E.

It is interesting that this same *5-HTT* gene variant *s* allele has been linked to increased amygdala reactivity (Dannlowski et al., 2007; Hariri et al., 2002, 2005) and altered amygdala connectivity to corticolimbic circuitry (Pezawas et al., 2005). Most recent findings suggest that the same serotonin transporter gene variant may increase anxiety sensitivity in the presence of maltreatment (Stein, Schork, & Gelernter, in press) and stress response through endocrine mechanisms (Jabbi et al., 2007). In favor of the *5-HTT* Gene Variant × Life Events interaction being a true finding, despite mixed evidence, the neuroimaging study results suggest plausible biological and cognitive mediating mechanisms. Finally, there have also been two very recent studies suggesting that a variant in a gene known as brain-derived neurotrophic factor (*BDNF*) that has been implicated as being affected by stress in animal studies also increases susceptibility to adverse life events, thereby increasing the risk for depression (Kauffman et al., 2006; Kim et al., 2007).

Antisocial behavior

Interest in links between a specific variant that affects function of the gene coding for the neurotransmitter degradation enzyme MAOA and antisocial behavior was fuelled by a report of an unusual family showing familial clustering of an *MAOA* gene mutation and aggression (Brunner, Nelen, Breakfield, Ropers, & Van Oost, 1993). There have been several studies suggesting that a functional *MAOA* gene variant is associated with antisocial behavior but only

in the presence of early family adversity (Caspi et al., 2002; Foley et al., 2004; Kim-Cohen et al., 2006; Widom & Brzustowicz, 2006). There have also been nonreplication findings published (Haberstick et al., 2005; Huinzinga et al., 2006). However, a recent study included a meta-analysis of all the published data to date and found significant evidence of G × E even when the original study by Caspi and colleagues (2002) was removed from the analysis (Kim-Cohen et al., 2006). Two of these studies investigated childhood maltreatment; the other used a related but different measure of early childhood family adversity (Foley et al., 2004).

Schizophrenia

The search for susceptibility genes that influence schizophrenia is now yielding replicated findings (Williams, Owen, & O'Donovan, 2007), but so far there have been relatively few molecular genetic studies investigating G × E. An exception is a finding that also initially came from the Dunedin cohort. Interest here focused on the gene encoding the enzyme COMT that is the primary mechanism responsible for clearing dopamine in the prefrontal cortex. A variant that affects enzyme function has been linked to prefrontal cortical function in several different studies (Tunbridge, Harrison, & Weinberger, 2005). Although this gene is a good candidate for involvement in the etiology of schizophrenia, evidence for association with this condition is equivocal (Williams et al., 2007). This, of course, theoretically makes it an attractive gene to examine when testing for G × E in schizophrenia. In the Dunedin study, the *COMT val/val* genotype that is associated with poor prefrontal cortical function was found to increase the risk for schizophrenia spectrum disorder among individuals with heavy early use of cannabis (Caspi et al., 2005). These findings have not been exactly replicated, but an experimental study of patients, relatives, and unaffected controls showed that individuals carrying the *val/val* genotype appeared to be more sensitive to showing delta-9-tetrahydrocannabinol (the active ingredient of cannabis) induced effects on psychotic experiences and cognition (Henquet et al., 2006).

ADHD

There have been many published molecular genetic studies of ADHD, and as a result, a number of meta-analyses have also been conducted (Faraone et al., 2005; Thapar, Langley, Owen, & O'Donovan, in press). Overall, the evidence implicates the likely involvement of a number of genes that code for proteins involved in dopamine pathways. Specifically, the strongest evidence to date from these studies shows evidence for small but significant association between a variant in the dopamine D4 receptor gene (*DRD4*). This marker corresponds to variation in the number of times a given DNA stretch of 48 bases is repeated sequentially, a so-called variable number tandem repeat (VNTR). The associated allele corresponds to seven copies of the repeat. The next most consistent set of evidence from different meta-analyses is for association between a dopamine D5 receptor gene marker and ADHD (Faraone et al., 2005; Thapar, O'Donovan, & Owen, 2005). The effect sizes of these risk variants are small (Thapar et al., 2007). There have also been many published studies investigating variants in the dopamine transporter gene (*DAT1*), but here the findings have been more mixed. Although there have been many replicated findings for *DAT1* and this goes against the likelihood of initial false positive results, whereas some meta-analyses have yielded significant evidence for association with one specific variant, others have not.

To date, most interest with regard to testing G × E for ADHD has focused on the candidate genes that have been most strongly implicated as being associated with ADHD; that is, variants in the dopamine D4 receptor gene and also the *DAT1* receptor gene and *DRD5* receptor gene. Although this might seem a good place to start, if one of the motivations to test G × E is to identify genetic variants that do no have main effects but that have risk effects in the presence of an environmental factor, these are not the ideal genes to be investigating. However, as mentioned earlier, genetic findings for *DAT1* have been mixed and here, G × E would be one plausible explanation for the inconsistent evidence for association across different studies.

DAT1

The first published study of G × E based on this gene included a North American population-based sample of children. The investigators tested for G × E between the *DAT1* genetic marker (a 480 base pair VNTR) previously implicated in ADHD and maternal smoking in pregnancy. There was significant evidence of G×E with children carrying two copes of the 10 repeat "risk" allele showing higher levels of hyperactive–impulsive symptoms (Kahn, Khoury, Nichols, & Lamphear, 2001). This finding was partially replicated in a US population-based sample of twins (Neuman et al., 2007). Here there was significant evidence of G × E between maternal smoking in pregnancy and *DAT1* contributing to *DSM-IV* ADHD. However, the interaction involved a different allele of the same marker, the 9-repeat allele. In contrast, two British studies from London and Cardiff that are based on clinical samples of children with ADHD have failed to find evidence of G×E for *DAT1* and smoking in pregnancy (Brookes et al., 2006; Langley et al., in press). The London study did, however, find evidence of interaction for maternal alcohol use in pregnancy, but this was with a previously unstudied DAT1 haplotype marker (combination of different marker alleles).

Finally, the most recently published study of a high-risk population sample found evidence for interaction between a composite measure of psychosocial adversity including factors such as marital discord, parental psychiatric disorder, and other family and parental adversity and two genetic markers in *DAT1* (Laucht et al., 2007). One of these markers was the most widely studied one (the VNTR), and the interaction was found with the putative risk 10/10 genotype.

Thus, there is some evidence to suggest possible G × E with regard to *DAT1*, which is a priori the most attractive candidate gene for ADHD as the dopamine transporter mechanism is inhibited by stimulant medication which is used to treat ADHD. However, results from different studies have so far been inconsistent in that G×E interaction has been found for different environmental risk factors (maternal smoking in pregnancy, alcohol use in pregnancy and psychosocial adversity), different genetic markers within this gene and different alleles. Moreover, unlike the studies on *MAOA* and antisocial behavior and *5-HTT* and depression, there are no compelling biological reasons for testing these specific interactions. The main argument for testing here has come about from the genetic studies where association of *DAT1* with ADHD has been inconsistent. However, inconsistency of findings for G × E should not necessarily lead to dismissal of its presence. If interaction is at the level of biological pathways then we may well expect multiple genes to interact with an environmental adversity, and that adversity may also be composed of different risk factors. For this scenario, the presence of G × E between a given variant and a given environmental risk will vary depending on the background genetic risk. Thus, the contribution of many other genes as well as other environmental contexts will be important. Moreover, gene function is unlikely to be captured simply by a single variant or indeed all variants within a given gene.

DRD4

The *DRD4* 7-repeat allele has been the most consistent association finding for ADHD. In contrast, findings of G × E for this gene have so far been inconsistent. The first study to investigate this found evidence of interaction between the *DRD4* marker and season of birth (Seeger, Schloss, Schmidt, Ruter-Jungfleisch, & Henn, 2004). A subsequent UK study also found evidence of interaction but in the opposite direction (Brookes et al., 2007). The US study of twins mentioned earlier for *DAT1* also found that those with the *DRD4* 7-repeat risk allele were more likely to show *DSM-IV* ADHD when exposed to maternal smoking in pregnancy (Neuman et al., 2007). However, this finding has not been replicated by our group in Cardiff (Langley et al., in press).

G × E Effects on the Developmental Course of ADHD

The etiological risk factors that contribute to the origins of ADHD could be the same as those that influence its developmental course. However, that is not necessarily the case (Thapar

et al., 2007). There is increasing evidence that both these scenarios are important for ADHD. Thus, as we have already considered, there is consistent evidence for association between the *DRD4* 7-repeat allele and ADHD. Two subsequent studies have suggested that the same risk allele also affects continuity of ADHD symptoms and diagnostic persistence (El Faddagh, Laucht, Maras, Vohringer, & Schmidt, 2004; Langley et al., in press). Another study found that the *DRD4* 7-repeat allele also influenced adult outcomes and functioning (Mill et al., 2006). The findings with regard to another gene, *COMT*, are different. As mentioned earlier, COMT is an enzyme that plays an important role in clearing dopamine in the prefrontal cortex. A functional variant in the *COMT* gene has been linked to prefrontal cortex (PFC) function. Given the evidence that PFC function is implicated in antisocial behavior and ADHD, this variant is a candidate gene variant for both conditions. In the Cardiff clinical sample of children with ADHD we found no evidence of association with the high risk *COMT val/val* genotype (Thapar et al., 2005). However, we did find evidence of association of this genotype with conduct disorder symptoms in children with ADHD. This finding has since been replicated in two other samples, both of which are population based (Caspi et al., in press) and in a pooled analysis of all published data (Caspi et al., in press), but not in a Canadian study (Sengupta et al., 2006). It is of interest that the findings to date suggest that the *val/val* genotype is associated with antisocial behavior in ADHD but not with antisocial behavior alone. Thus, it appears that the *COMT val/val* genotype affects a key developmental outcome in ADHD, notably antisocial behavior.

In the Cardiff ADHD genetic study, although no effects of G×E have been detected for *DRD4*, *DRD5*, and *DAT1*, they have been found to contribute to antisocial behavior in ADHD (Langley et al., in press). First, we found interaction between maternal smoking during pregnancy and markers in *DAT1* (VNTR) and *DRD5* in influencing antisocial behavior symptoms in ADHD (Langley et al., in press). Second, lower birth weight was found to show interaction with the *COMT val/val* genotype and the *DRD5* receptor gene variant previously implicated in ADHD in increasing conduct disorder symptoms in ADHD (Langley et al., in press; Thapar et al., 2005). There was evidence to suggest that those with ADHD possessing the *COMT val/val* genotype and the putative *DRD5* risk allele were more sensitive to the adverse effects of a lower birth weight, and those exposed to both risk factors showed higher conduct disorder symptoms (Langley et al., in press; Thapar et al., 2005). There were not only main effects of the *COMT val/val* genotype on early onset conduct disorder symptoms (a finding since replicated) and lower birth weight but also significant evidence of G × E. However, until these interaction findings are replicated, they should be regarded with caution but are highlighted as a reminder that it becomes important to separately consider the contribution of G × E to the developmental course of ADHD. Even where G×E does not appear to contribute to the initial development of the disorder, it may have a modifying effect on the developmental course and outcomes.

Pharmacogenetics of ADHD—An Example of G × E

The focus of pharmacogenetics is to identify genetic variants that influence clinical response to medication or affect susceptibility to side effects. It represents a potentially important type of G×E in that findings could potentially influence clinical practice. In this instance, the prescribed medication is the environmental factor. ADHD is a condition where medication has been shown to be effective with around 70–80% of children showing symptomatic benefits notably with stimulant medications such as methylphenidate and dexamfetamine (MTA Co-operative group, 1999). Atomoxetine is a newer medication that primarily affects the norepinephrine transporter mechanism. There has been considerable interest in identifying gene variants in children with ADHD that predict clinical response to these medications. These types of studies have not only investigated genes involved in neurotransmitter systems, but also variants that influence pharmacokinetics, essentially the body's way of absorbing, distributing, and getting rid of medication. For example, many but not all psychotropic medications are metabolized by cytochrome p450

enzymes in the liver. There are well-known individual differences in enzymatic activity, and in some instances quite marked ethnic differences. For example, atomoxetine is metabolized by the P-450 2D6 (CYP2D6) enzyme pathway and a recent study suggested, as might be expected, that poor metabolizers showed greater treatment response but more side effects in terms of effects on blood pressure, pulse, and weight (Michelson et al., 2007). There has been interest across medicine in testing whether specific variants affecting such enzymes influence treatment response and side effects. In the case of ADHD, pharmacogenetic research is at an early stage, and there are no consistent findings that are yet likely to influence clinical practice. Thus far, most interest has focused on *DAT1* and response to methylphenidate, but findings have not been consistent. However, until very recently, studies have not been based on randomized controlled trials. One exception is a recent study that suggested that a variant in the adrenergic alpha-2a receptor gene influenced the response of inattention symptoms to methylphenidate (Polanczyk et al., 2007), although replication findings are required. This area represents new research that complements G × E investigation, but it is nonetheless important within the context of the present review.

Bringing It All Together: What Can We Conclude From G × E Investigation?

That genes and environment work together in complex ways is now undisputed. It is thus only natural that current interest has turned to investigating the contribution of G × E to psychopathology. This interest is occurring against a context where molecular genetic studies aimed at identifying susceptibility genes for complex disorders including psychiatric disorders/psychopathology have become large scale and are beginning to yield replicated findings. As has been the case for many years for researchers interested in environmental risk factors, moving from established association to confirming causality is challenging.

The term G × E can mean different things to different people, and this has often resulted in heated debate. There are also a number of different research designs that are being used to investigate G × E, and the interpretation of the results from each of these designs naturally varies.

Despite these issues and methodological challenges, the importance in investigating G × E is increasingly being recognized by individual researchers and national bodies (Institute of Medicine, 2006). Despite skepticism from some quarters—and there is the necessity for caution, especially because in the field of genetics there has been a history of unrealistic enthusiasm about new approaches—findings of G × E are being replicated. Results from different types of study design are surprisingly, in some instances, converging. In our view, so far the contribution of G × E is most convincing with regard to antisocial behavior and depression, but effect sizes are small. Future studies will be crucial in providing further evidence.

Examining G × E is important with respect to understanding more about the etiology of disorders and life course psychopathology. However, not all genes will interact with environmental factors, and we do not agree that genetic studies are not at all useful unless environmental risk factors are incorporated. For very large-scale gene identification studies this may not be feasible, and assessing environmental factors accurately and appropriately for large sample sizes is expensive. However, it is important that genetic findings from such studies are then used to inform environmentally focused research where proper measures are available.

Other important considerations are the likely small effect sizes of risk factors including G × E contributions such that large sample sizes are likely to be needed and the issue of multiple testing. Replication and meta-analyses thus become crucial. Researchers need to adopt similar measurement strategies when defining risk factor and outcome at the outset to enable this process.

The focus of this article and most published G × E research has been on risk factors. However, the contribution of protective factors is also important and has so far been relatively neglected, although there are some exceptions. For example, one study (Kaufman et al.,

2006) that replicated findings of G × E for exposure to life events and possession of the *5-HTTLPR* short allele, found that social support ameliorated risk effects on depression. Future research on G × E by definition will need to expand its focus beyond risk to resilience and will by the very nature of the research questions under study necessitate "interaction" across disciplines (Cicchetti, & Blender, 2004, 2006). The contribution of G × E to resilience will likely operate at multiple levels and influence the processes leading to resilience in different and complex ways (Cicchetti & Blender, 2004, 2006). Both genetic and environmental factors are likely to contribute protective effects. Thus, for example where G × E has been detected for a specific genetic variant, it may be that the genetic variant confers protective effects in the face of stress and adversity. Another potential scenario is where an allelic variant is a risk factor for psychopathology in one environmental context but confers protection in an alternative context. Disentangling risk from nonrisk genetic factors as they relate to or interact with risk and protective factors unique to the social environment offers significant challenge at both conceptual and methodological levels. However, if G × E is to be functionally understood as a contributing or causal element in the etiology of psychopathology, disentangling the interplay between multilevel constellations of genetic and environmental risk and protective factors must be pursued. Doing so will facilitate significant progress toward the development of an improved empirical basis that can inform risk reduction intervention strategies for those at higher genetic risk of developing specific conditions.

The study of G × E offers significant challenges, challenges that cannot be answered by one discipline alone. The interdisciplinary domain of developmental psychopathology offers a theoretical framework for the study of G × E that explicitly recognizes the equifinality and multifinality of processes at play in understanding variation in normal and abnormal psychological development. We hope this article goes some way toward further elucidating the present state of research relating to the interplay between genetic factors and specific environmental factors with respect to the specific phenotypes considered throughout this review.

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