The Cutting Edge

GENE–ENVIRONMENT INTERPLAY

Michael Rutter is professor of Developmental Psychopathology at the Institute of Psychiatry, King's College London. His research interests span a wide field, but have a particular focus on the developmental interplay between nature and nurture, and on the use of natural experiments to test causal hypotheses about genetic and environmental mediation of risk in relation to normal and abnormal psychological development. He is the recipient of numerous international awards and honors, and was elected a Fellow of the Royal Society in 1987, and was a founding fellow of the Academia Europaea and the Academy of Medical sciences. He has published over 40 books and 400 scientific articles.

Traditional quantitative behavioral genetics was concerned with partitioning the population variance for particular traits (or disorders) into genetic (separating additive and synergistic effects) and environmental components (separating shared and nonshared effects). Although there was undoubted value in the findings, it is now clear that the approach constituted a misleading oversimplification because it assumed that the components had to add up to 100%, thereby ignoring gene–environment co-action. Such co-action takes several different forms, and this commentary will largely focus on gene–environment interaction ($G \times E$), but first it is necessary to note several other forms of co-action.

To begin with, there are gene–environment correlations (rGE), meaning genetically influenced individual variations in exposure to risky or protective environments.[1,2] Geneticists sometimes tend to discuss this topic as if the main issue concerns the genetic effect, but this is misleading. The proximal mechanism concerns the role of people's behavior in shaping or selecting environments—indicated by both longitudinal studies that showed the effect of disruptive behavior in childhood on the rate of acute and chronic life experiences in adult life that have been demonstrated to play a role in the liability to depression,[3,4] and behavioral genetic studies that showed the effects of children's behavior on the behavior of adoptive parents.[5,6] Of course, the behavior will have been genetically influenced (hence the rGE), but that issue is secondary to the need to study how the specific behaviors of individuals influence the shaping and selecting of environments. With respect to depression and anxiety, the key focus is on the fact that environments are not randomly distributed. Social selection means that there needs to be a concern regarding the origins of risk environments as well as focus on their effects.

A different form of co-action is provided by environmental effects on gene expression.[7,8] Environments cannot alter gene sequences, but genetic effects are dependent on the expression of genes; this process has been shown to be influenced by both environmental influences and chance variations. In this way, there can be relatively strong environmental moderation of genetic effects. It has not been easy to study this in humans because such expression tends to be relatively tissue-specific and developmental phase-specific, but it is known (from post-mortem studies) that environmental modification of gene expression does take place.

ENVIRONMENTAL EFFECTS

Twin studies have been consistent in showing that, for almost all traits (including depression and anxiety), environmental influences account for a substantial proportion of the population variance—for some traits more than half.[9] Natural experiments, too, have confirmed the importance of environmentally mediated causal influences stemming from both early environmental features (such as sexual assault and physical abuse) and more immediate onset-provoking negative life events carrying long-term threat.[10,11] However, even with unusually severe and prolonged deprivation, there is considerable heterogeneity in response. This has been evident in both naturalistic and experimental studies of humans and animal models.[12] That universal finding raises the question of whether at least part of that heterogeneity derives from genetic influences on environmental susceptibility.[13]

*Correspondence to: Michael Rutter, MRC SGDP Center, PO 80, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF. E-mail: Camilla.azis@kcl.ac.uk

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BIOLOGICAL EXPECTATIONS OF G × E

Before considering the empirical evidence, it is necessary to consider whether an understanding of biology leads to an expectation that G × E should be common or extremely rare. It is clear that G × E is to be expected because: (i) to suppose that G × E is rare would imply that susceptibility to the environment is almost the only biological feature outside the influence of genetics; (ii) it would cast doubt on the fundamentals of evolutionary theory in which genetically influenced variations in response to the environment constitute the key mechanism; and (iii) it would have to assume that genetics played no role in the well-documented, huge heterogeneity in responses to all manner of environments.[14] In addition, it should be added that there is substantial evidence of G × E in the field of somatic medicine.[13,15]

In the light of these background considerations, it might seem surprising that some behavioral geneticists have expressed extreme skepticism about the existence of G × E in the field of psychopathology.[16,17] The most obvious and straightforward reason is that they have focused exclusively on G × E as a statistical concept concerned only with a multiplicative, synergistic interaction using a logarithmic scale. The origins can be found in the famous dispute between Fisher and Hogben.[18,19] Fisher, the originator of much of the modern statistics, tended to regard G × E as a 'nuisance' term to be eliminated by means of appropriate statistical scaling manipulations, in order to get on with the serious business of partitioning the population variance into genetic and environmental components. Hogben, a biologist as well as a statistical mathematician, argued that the focus had to be on biological interactions if there were to be health benefits deriving from an understanding of the biological pathways involved. Both Fisher and Hogben agreed, nevertheless, that there were crucial statistical issues and problems that had to be dealt with in order to elucidate the biology. Tabery correctly concluded that Hogben was right. The insistence on using a logarithmic scale was also misguided, because most researchers consider that additive synergistic interactions better match the biological concepts.[14]

IDENTIFIED SUSCEPTIBILITY GENES AND MEASURED ENVIRONMENTS

The situation with respect to G × E in humans was transformed by the technological advances that allowed the study of individual susceptibility genes and measured environments.[8] The initial key scientific findings, derived from the Dunedin longitudinal study undertaken by Caspi, Moffitt, and their colleagues and the particular finding directly relevant to anxiety and depression, concerned the interaction between allelic polymorphic variations of the serotonin transporter promoter (5-HTTLPR) and either childhood maltreatment or multiple life events.[20] Specifically, the short (s) variant was associated with a significantly increased likelihood of depression after early maltreatment or multiple negative life events in the immediate preceding 5 years (but not with an increase in the absence of these circumstances). The focus on 5-HTTLPR was determined by the extensive evidence in humans and other animals that serotonin metabolism is implicated in the liability to affective disorders.[20,21]

Given the necessary concerns regarding crucial methodological checks, attention needs to be paid to the steps taken in the Dunedin study. First, the possibility of artifact stemming from scaling features was dealt with in three steps: (i) demonstration that the G × E applied to a range of different measures with different scaling properties; (ii) demonstration that the G × E was found with a polymorphism sharing the same scaling as the 5-HTTLPR polymorphism, but not its biological properties; and (iii) demonstration that the G × E did not apply to other psychopathological outcomes (such as antisocial behavior). Second, the possibility of an interaction that reflected rGE rather than G × E was dealt with by showing that the 5-HTTLPR polymorphism was not associated with exposure to either maltreatment or multiple life events. Third, the possibility that the interaction reflected a gene–gene synergism rather than G × E was dealt with by showing that the G × E did not apply to life events occurring after the onset of depression. The rationale was that, whereas the causal effect of E could only apply to E before the onset of depression, there was every reason to suppose that a gene–gene interaction should apply both before and after onset.

However carefully any study has been done, the crucial test has to be whether the findings can be replicated in other samples investigated by independent researchers. Uher and McGuffin[22] located 34 human observational studies published up to the end of March 2009. There were 17 positive replications of the original G × E finding in the expected direction, eight partial replications (such as an interaction only in females or only with one of several types of environmental adversity), and nine non-replications (meaning no G × E or an interaction in the opposite direction). The partial replications and non-replications were preponderantly found in adolescent samples ($P = .02$). It was even more striking that all studies using objective measures or structured interviews replicated the G × E wholly or partially, whereas all non-replications relied on brief self-report measures of environmental adversity. It may be concluded that sampling and measurement variations accounts for most of the variations in findings. Moreover, the extent of positive replications is very impressive and stands in sharp contrast to the usual prevalence of non-replications in psychiatric molecular genetics. Nevertheless, it would be premature to conclude that a truly adequate understanding of the variation in findings has been achieved.

Brown and Harris[23] have raised two rather different issues. First, they noted that the life event (LE) findings

apply to events over a five year period—a time span out of keeping with the much narrower time window for the role of a major LE in provoking the onset of depression.[24] They concluded that this suggests that multiple life events serve as a marker for child maltreatment which may be the true E agent. Second, they suggested that the G × E may mainly apply to an adult onset of depression taking a chronic course.

It is necessary now to turn to the Risch et al.[1] meta-analysis which claimed that the strongly negative results of their meta-analysis put the 5HTTLPR G × E finding in serious doubt. There are six main reasons for questioning this sweeping dismissal.[14] First, the meta-analysis was based on just 13 of the 34 relevant studies (plus one for which no relevant reference was provided). Uher and McGuffin[22] showed that the 14 studies included were significantly ($P<.02$) biased toward negative studies. Second, the recoding of the original data transformed some positive findings in the original reports to negative, with no explanation being provided as to how that came about. Third, the meta-analysis dealt only with LE and not maltreatment. Fourth, a strong claim was made that all studies of G × E must start with a statistically significant main effect for the genetic polymorphism. This ignored the fact that statisticians are divided on the merits and demerits of testing for main effects before interactions, or the reverse. Fifth, they focused exclusively on multiplicative interactions using a logarithmic scale. Sixth, and most crucially, they treated G × E as a purely statistical finding, ignoring the substantial positive biological findings.

BIOLOGICAL STUDIES

Thus, they paid no attention to the human experimental studies using brain imaging to examine the neural concomitants of G × E with respect to 5-HTTLPR and response to fear-evoking stimuli—a clinically relevant endophenotype.[25–27] Notably, these neural findings applied to individuals without psychopathology. This meant that there was no genetic main effect on depression that could operate in this deliberately chosen sample, which did not have a depressive disorder. Even more importantly, the findings meant that the pathogenic risk operated indirectly, being evident in normal individuals, although playing some role in the biological pathway leading to depression. The Risch et al.[17] article also ignored the published meta-analysis of the 5-HTTLPR association with amygdala activation[26] and the meta-analysis of the association with selective serotonin reuptake inhibitor efficacy in patients with depression.[28] Finally, the Risch et al.[17] article ignored the similar G × E findings in rhesus monkeys when treating peer rearing as the relevant environmental adversity,[29–31] or the gene knock-out mouse model showing a difference in hormonal response to stress according to the serotonin transporter gene. Taken together with the basic science findings on serotonin metabolism, there would seem to be a strong case for the likelihood of a valid G × E effect operating on a biological pathway relevant in the genesis of depression. Uher[32] has suggested that the G × E may bring about biological changes through epigenetic mechanisms operating most strongly in early life. If that proved to be the case, it would seem to favor maltreatment, rather than LE, as the key E hazard (although that has yet to be tested). Why this may be less evident in the case of adolescent-onset depression remains unclear but, possibly, it may reflect the major endocrine and life experience changes during this age period.[33]

CLINICAL IMPLICATIONS

Whilst it is too early for the G × E findings to have direct clinical implications, it is not too early to consider the possible clinical implications of G × E. First, the findings provide leads on the possible ways in which environments "get under the skin." If adverse environments have enduring effects that persist beyond the negative experience (and there is evidence that in some circumstances they do), the mediating mechanism must involve some kind of biological effect (although whether this concerns epigenetics or neuroendocrine mechanisms or altered mental models remains to be determined). Second, the human experimental findings indicate that the mediation operates on biological pathways that are general in the population and not specific to mental disorders. Third, however, the effects are relatively specific to certain forms of psychopathology. Fourth, the G × E implies (although does not prove) that the biological pathway for E effects overlaps with the biological pathway for G effects. In other words, the main clinical benefit is likely to come from an elucidation of the biological pathways.

Nonetheless, Uher[32,34] has argued that the G × E findings may already be relevant to the well demonstrated heterogeneity in individual responses to treatment of affective disorders. Perhaps, pharmacological treatments may be more effective in individuals with environmentally insensitive genotypes and psychological interventions in those with environmentally sensitive genotypes. It is too early to know whether this hypothesis will be upheld, but the key point is that whilst undertaking the various types of research needed to clarify the biological mechanisms underlying G × E, it may still be appropriate to move into translational mode,[35] both not only because the findings might improve clinical practice but also because they may be informative on the biology.

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