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Probabilistic epigenesis

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Abstract

The notion that phenotypic traits, including behavior, can be predetermined has slowly given way in biology and psychology over the last two decades. This shift in thinking is due in large part to the growing evidence for the fundamental role of developmental processes in the generation of the stability and variations in phenotype that researchers in developmental and evolutionary sciences seek to understand. Here I review the tenets of a metatheoretical model of development called probabilistic epigenesis (PE) and explore its implications for furthering our understanding of developmental and evolutionary processes. The PE framework emphasizes the reciprocity of influences within and between levels of an organism's developmental manifold (genetic activity, neural activity, behavior, and the physical, social, and cultural influences of the external environment) and the ubiquity of gene–environment interaction in the realization of all phenotypes.

Introduction

The developmental mode of analysis is the only method that can truly explain the structures and functions of maturing and mature organisms. This is an insight that dates back to the resolution of the epigenesis-preformation debate in the 1700s. The crux of the notion of developmental analysis was succinctly stated by Caspar Friedrich Wolff in his great 1764 treatise on embryological development of the chick: '. . . each part is first of all an effect of the preceding part, and itself becomes the cause of the following part' (cited in Hall, 1999, p. 112). The singularly important role of developmental analysis took a great leap forward in the late 1800s with the establishment of experimental embryology by Wilhelm Roux (reviewed in Gottlieb, 2002a), in which normal development was systematically perturbed to get an understanding of what was called the 'mechanics of development' (*Entwicklungsmechanik*). The latter term was used by Roux to describe a new science of causal morphology, i.e. an investigation of the development of form, not the mode of action of an already formed mechanism (reviewed in detail by E.S. Russell, 1917).

For the present purposes, the results of the various experimental manipulations of the embryo and its developmental context are of extreme importance. The various manipulations of the early embryo typically caused different outcomes of development, thus giving rise to two significant metatheoretical concepts: *Reaction potential* and *interaction*. Reaction potential referred to the heredity of the organism, bits and pieces of which were revealed depending upon the specific interactive influences that were allowed, or made experimentally, to operate during embryonic development. Today in developmental biology, the term *epigenetics* has come to refer to 'the control of gene expression by the environments and microenvironments encountered by embryos or parts of embryos . . .' (Hall, 1999, pp. 113–114). So, in developmental biology the ubiquitousness of interaction is taken for granted and extends to the activation of genetic activity by nongenetic influences, not just the formative influences of cell–cell, tissue–tissue, and organ–organ interactions. It makes good sense to extend this point of view to developmental psychobiology and, with some added refinements, that is what the author has been attempting to do with the metatheoretical model called *probabilistic epigenesis*.

Probabilistic epigenesis

Probabilistic epigenesis is to be contrasted with predetermined epigenesis, the latter holding that genetic activity gives rise to neural (and other) structures that begin to function when they become mature in the unidirectional sense of genetic activity → structure → function. In contrast, in line with the evidence now available at all levels of analysis, probabilistic epigenesis holds that there are bidirectional influences within and between levels of analysis

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* Regrettably, Gilbert Gottlieb died shortly after submitting an earlier version of this paper to the journal. Some changes to the text were made by Bob Lickliter in response to editorial comments from the editors of the journal.

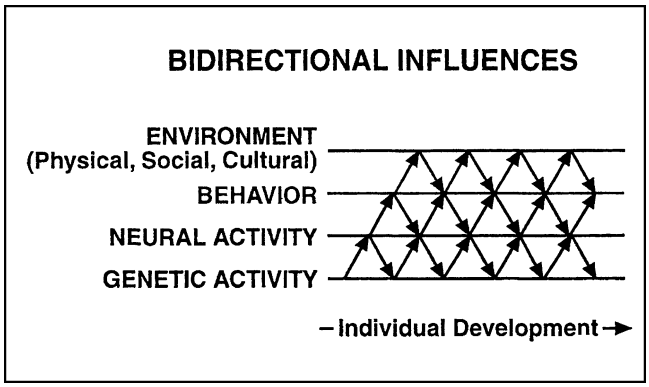

Figure 1 *Metatheoretical model of probabilistic epigenesis: Completely bidirectional influences over four levels of analysis (genetic activity, neural activity, behavior, physical, social, cultural aspects of environment). Reprinted with permission from Gottlieb, 2002c.*

so that the appropriate formula for developmental analysis becomes genetic activity → structure → function. In this view, neural (and other) structures begin to function before they are fully mature and this activity, whether intrinsically derived ('spontaneous') or extrinsically stimulated (evoked), plays a significant role in the developmental process.

Since the coordination of formative functional and structural influences within and between all levels of analysis is not perfect, a probabilistic element is introduced in all developing systems and their outcomes. The fully sketched model, including behavior and extra-organismic environmental influences, is shown in Figure 1.

The biggest obstacles in getting the probabilistic-epigenetic model understood and accepted by biologists, neuroscientists, and social scientists concerns (1) its view of the role of genes in the developmental process, (2) implementing the PE framework in ongoing research, including the reciprocity (bidirectionality) of influences within and between the four levels of analysis (genetic activity, neural activity, behavior, the physical, social, and cultural influences of the external environment), and (3) a seemingly unorthodox take on the concept of interaction, particularly the ubiquity of gene–environment interaction. There is some necessary overlap in these three issues but I will discuss them in turn.

Role of genes in the developmental process

The fact that DNA is an inert molecule means that genes can't turn themselves on and off; they require intracellular signals, some of which originate from outside the cell and, indeed, outside the organism. The claim of the central dogma of molecular biology is that proteins are made by the predetermined unidirectional formula DNA → RNA → Protein, in which case the genes would be pictured as the unmoved movers of development. (The DNA → RNA relation is called transcription and the RNA → Protein relation is called translation.) The truth of the matter is that proteins can and do act on RNA and on DNA, and that in the most dramatic case RNA can transform DNA by a process called reverse transcription. In terms of attempting to correlate genes with developmental outcomes at the neural and behavioral levels, we need to constantly remind ourselves of the uncertainty involved. Since much of the genetic analysis in humans involves single nucleotide polymorphisms (SNPs), which are merely markers for as yet unidentified genes, RNA-editing adds a further complication in trying to specify the involvement of specific genes in neural and behavioral outcomes. One human gene may produce up to five different proteins as a result of alternative splicing (Peters & Boekholdt, 2002).

I believe it is essential to adopt a probabilistic epigenetic framework in attempting to correlate genes (and their markers) with neural and behavioral outcomes. The reason this is necessary is that genes are not exempt from influences at other levels of analysis but are, in fact, dependent upon them for initiating and terminating their activity. And when I say 'probabilistic epigenetic framework', I do not mean merely the DNA → RNA→ Protein level of analysis but the other three levels as well. There is considerable evidence that genetic activity is influenced by neural, behavioral and external environmental events, and the results of a number of those studies are summarized in Table 1.

The failure to replicate genetic studies of psychopathology, as well as genetic → neural outcomes, is legion, and those numerous failures should be taken as a datum. For example, in reviewing over 200 studies of the involvement of polymorphisms in dopamine receptors, the latter known to be involved in a number of disorders, Wong, Buckle and Van Tol (2000, p. 194) came to these conclusions:

> The myriad, conflicting results of association and family linkage studies cannot be easily summarized. There is essentially no clear-cut case in which polymorphisms in any of the dopamine receptor genes are related to neuropsychiatric disorders, or even to a specific phenotype. . . . This uncertain picture is not unique to the pharmacogenetics of dopamine receptors, as a similarly confusing scenario is found in many complex genetic diseases, including some that have been discussed in the review such as schizophrenia and bipolar disorder.
>
> The fundamental issue may be that dopamine receptors are only one component of the array of neurotransmitter receptor systems that influence behavior in concert with genes that control neurodevelopment, connectivity, neuronal signaling, and synaptic plasticity.

Table 1 *Normally occurring environmental and behavioral influences on gene activity*

Species	Environmental signal or stimulus	Resulting alteration
Nematodes	Absence or presence of food	Diminished or enhanced neuronal *daf-7* gene mRNA expression, inhibiting or provoking larval development
Fruit flies	Transient elevated heat stress during larval development	Presence of proteins produced by heat shock and thermotolerance (enhanced thermal regulation)
Fruit flies	Light-dark cycle	Presence of PER and TIM protein expression and circadian rhythms
Various reptiles	Incubation temperature	Sex determination
Songbirds (canaries, zebra finches)	Conspecific song	Increased forebrain mRNA
Hamsters	Light-dark cycle	Increased pituitary hormone mRNA and reproductive behavior
Mice	Acoustic stimulation	Enhanced c-*fos* expression, neuronal activity, and organization of the auditory system
Mice	Light-dark cycle	c-*fos*-induced mRNA expression in hypothalamus, circadian locomotor activity
Rats	Tactile stimulation	Enhanced c-*fos* expression and increased number of somatosensory (sense of touch) cortical neurons
Rats	Learning task involving vestibular (balance) system	Change in nuclear RNA base ratios in vestibular nerve cells
Rats	Visual stimulation	Increased RNA and protein synthesis in visual cortex
Rats	Environmental complexity	Increased brain RNA diversity
Rats	Prenatal nutrition	Increase in cerebral DNA (increased number of brain cells)
Rats	Infantile handling; separation from mother	Increased hypothalamic mRNAs for corticotropin-releasing hormone throughout life
Cats	Visual stimulation	Increased visual cortex RNA complexity (diversity)
Humans	Academic examinations taken by medical students (psychological stress)	Reduced mRNA activity in interleukin 2 receptor (immune system response)

Note: mRNA = messenger RNA; PER and TIM are proteins arising from *per* (*period*) and *tim* (*timeless*) gene activity; activity of c-*fos* genes leads to production of c-FOS protein. References documenting the findings listed can be found in Gottlieb, 1998 (Table 2).

This strictly unidirectional, bottom-up approach advocated by the authors in the second paragraph of their quote, while prevalent in this area of study, will not solve the problem: The recognition of the bidirectionality of influences and the involvement of the behavioral and environmental levels of analysis will have to be included in order to successfully link genes and nervous system to developmental-psychopathological (and other) outcomes. If this more comprehensive analytic framework is not implemented, I believe there will be continued failures of replication between genotypes and neural and behavioral outcomes, whether psychopathological or otherwise.

Implementing the probabilistic-epigenetic framework

Given the present state of the art and science of the various disciplines involved, implementing the PE framework will necessarily be a piecemeal affair. We not only have the four levels of analysis to deal with but the reciprocity (bidirectionality of influence) among them. We need to be opportunistic in seeking out transdisciplinary collaborations and taking advantage of those that present themselves. Where it has been possible to implement the PE framework, even in a piecemeal fashion, the results have been promising. I take it as a given that genes, in

and of themselves, cannot produce any neural or behavioral outcome and that gene–environment interaction is a requirement of normal as well as abnormal development. (I critically discuss the thorny issue of the statistical concept of gene–environment interaction in the next section.) Thus, the PE model of developmental outcomes assumes that individuals of the same genotype can have different neural and behavioral outcomes according to the *dissimilarity* of their relevant life experiences, broadly construed. I think this is the basis for the lack of replications among studies that look only at genotypes and attempt to correlate a particular genotype with a certain neural or behavioral outcome without looking for the presence or absence of intervening life experiences that may be crucial to the presence or absence of the outcome. Take the much-studied inhibitory neurotransmitter serotonin. Low levels of serotonin are associated with depression and alcohol abuse in humans. However, correlates of low serotonin are not behaviorally specific (i.e. low serotonin is involved in a number of psychiatric disorders). In rhesus monkeys, low concentrations of serotonin metabolites (collected from cerebral spinal fluid) are associated with higher levels of impulsive aggression and risk taking (Suomi, 2000). Rhesus infants who develop the least secure attachment with their mothers are also the most likely to have deficits in their central serotonin metabolism. Because there is a positive correlation between maternal and infant serotonin level, a genetic deficit could be involved, but it is possible that aberrant maternal care may make a necessary contribution to the serotonin deficit. To shed light on the genetic and interactive aspect, Bennett *et al.* (Bennett, Lesch, Heils, Long, Lorenz, Shoaf, Champoux, Suomi, Linnoila & Higley, 2002) genotyped the monkeys in Suomi's laboratory for a known polymorphism (long and short allele) in the serotonin transporter gene (5-HTT). The short allele confers low transcriptional efficiency to the 5-HTT gene promoter (relative to the long allele), so low 5-HTT expression may result in lower serotonergic function. However, evidence for this in humans is inconsistent because the necessary life experience correlates have not been examined. In the case of rhesus monkeys, when attempting to correlate the genetic polymorphism to serotonin metabolism, serotonin concentration did not differ as a function of long or short 5-HTT status for mother-reared monkeys, whereas among peer-reared monkeys, individuals with the short allele had significantly lower serotonin concentrations than those with the long allele. Thus, the lowered serotonin metabolism was not simply a consequence of having the short allele but required the life experience of peer rearing in this instance. This result supports my idea that the inconsistencies in the human literature are likely due to unknown but influential differences in the experiential histories of the populations under study.

Thus, the notion that the short allele of the 5-HTT gene is inevitably associated with a CNS deficit or defect is not true: The neural outcome depends on the developmental rearing history of the animal, as well as the particular genotype of the animal itself, what has elsewhere been termed 'relational causality' (Gottlieb & Halpern, 2002). The present finding most likely also explains why there are inconsistencies in the human literature in finding anxiety-, depression- and aggression-related personality traits associated with variations in the serotonin transporter gene. The association, or lack thereof, does not simply reflect genetic causality but developmental-relational causality.

Turning to a similar example concerning the development of psychopathological behavior, a functional polymorphism in the promoter of the monoamine oxidase A (MAOA) gene is or is not associated with conduct disorder, violent offenses, disposition toward violence, and antisocial personality disorder depending on whether or not the adult person was maltreated in childhood (Caspi, McClay, Moffitt, Mill, Martin, Craig, Taylor & Poulton, 2002). Once again, because of the failure to recognize the generality of the necessity of gene–environment interactions in producing outcomes, 'Evidence for an association between MAOA and aggressive behavior in the human general population remains inconclusive' (Caspi *et al.*, 2002).

The results of the Caspi *et al.* study support the present model of probabilistic epigenesis in that, when the children with the short form of the MAOA polymorphism are reared under conditions of no maltreatment, probable maltreatment, or severe maltreatment, it is only the latter group in which a substantial number (85%) exhibit some form of the four aggression measures listed above. Alternatively, having the long form of the genotype ('high MAOA activity') significantly reduces the probability of the development of antisocial behavior even under conditions of severe maltreatment.

This study shows very clearly that a knowledge of genotype and the presence or absence of an influential life experience provide indispensable aids to understanding the likelihood of an antisocial outcome in the face of maltreatment in childhood. This is another good example of relational causality, as well as the value of the piecemeal implementation of the probabilistic-epigenetic framework. Much remains to be done, but it is a valuable first step. Since it is widely recognized that many genes (and more than one life experience) contribute to the same behavioral outcome, we would like to suggest that the next important step in the strategy for doing developmental behavioral genetics research will be to include more than one gene and more than one life experience in

such studies. Otherwise, the plethora of non-replications that haunt this area of research, especially the one gene–one outcome 'association' studies, are apt to plague the one gene–one life experience approach. Although studies such as Caspi *et al*. would seem more likely to be replicated because they include a specific life experience (Foley, Eaves, Wormley, Silberg, Mals, Kuhn & Riley, 2004), they, too, have already been shown to be subject to non-replication (Haberstick, Lessen, Hopfer, Smolen, Ehringer, Timberlake & Hewitt, 2005). Thus, the obvious next step is to move to a multiple gene–multiple life experience approach (Gottlieb, in press). Another important aspect of the multiple gene–multiple life experience approach is that one can get statistically significant results with much smaller sample sizes than is usual in behavioral genetics research using traditional methods.

Another important aspect of implementing the PE model is being alert to the reciprocity or bidirectionality of influences within and between the four primary levels of analysis in Figure 1. The documentation of bidirectionality is much easier in animal research than in human research because of the possibility of doing the necessary experimental manipulations in animals. Nonetheless, reciprocity has been observed across three levels in some developmental-psychobiological studies of psychopathology. Let us first take a common environment → behavior example, which begins with the observation that intrusive mothers of 3-month-old infants are likely to have insecurely attached children at 1 year (Lewis, 1990). The bidirectional component is that the mothers' overstimulation is related to their child's behavior in children who are not socially oriented at 3 months of age, i.e. those who prefer to play with and look at toys rather than people. These children often have mothers who are overstimulating and the result is an insecurely attached child. In this example, the parent's behavior affects the child's behavior but the parent's behavior was affected by the child's earlier behavior. Documenting such circular social-developmental patterns, wherein child causes affect the environment and environmental causes affect the child, presents analytic difficulties:

> Such models have intrinsic appeal, but by their nature are difficult to test. Nonlinearity requires a mathematics that still eludes us. Moreover, it is difficult not to treat a child or an environmental characteristic as a 'pure' quantity even though we might know better. (Lewis, 1990, p. 25)

Ubiquity of gene–environment interaction in individual development

The organism–environment interrelationship is at the heart of developmental biology as well as developmental psychology. It is ironic that until the advent of high-level statistical tools such as the analysis of variance and the concomitant statistical estimates of heritability, the omnipresence of gene–environment interactions, called the *norm of reaction* in biology, was taken for granted. In 1909, Woltereck introduced the notion of the norm of reaction to operationally and experimentally define Johannsen's (1909) newly coined concepts of gene, genotype, and phenotype. However, Woltereck, while acknowledging the general utility of Johannsen's constructs, felt that Johannsen's concept of genotypic influences on phenotypic outcomes under different rearing circumstances was incorrect. Woltereck portrayed Johannsen's understanding of phenotypic development as what Gottesman (1963) introduced into psychology as a reaction range – the preservation of relative phenotypic differences between different genotypes across a number of rearing environments (the more or less parallel lines on the left side of Figure 2 – Gottesman's depiction is shown in Figure 4). The insufficiency (i.e. the lack of generality) of the reaction-range concept, in contrast to the norm of reaction, will be discussed below.

When Woltereck experimentally examined the influence of three different quantities of nourishment on the development of head size (helmet height) in three geographic varieties of the freshwater crustacean daphnia (*Hyalodaphnia cucullata*), he obtained three very different curves in moving from the deprived through the normal to the enriched conditions of nutrition, as shown on the right side of Figure 2. Woltereck regarded the outcomes of these kinds of developmental experiments – ones designed to empirically determine the phenotypic curves for a range of rearing conditions in closely related but genetically distinct groups – as defining what Johannsen called the genotype. The generality of Woltereck's concept of the unpredictability of the phenotype of similar genotypes when confronted with novel rearing circumstances has been validated repeatedly in psychology, as well as in biology, down to the present day, and these results conform to the notion that epigenetic outcomes are probabilistic rather than predetermined (Gottlieb, 1970, 1991). For example, one of the most ambitious studies of reaction norms examined the number of bristles, viability, and development time in 32 strains from three different natural populations of fruit flies (*Drosophila pseudoobscura*) at two egg densities and three temperatures (Gupta & Lewontin, 1982). They found a considerable number of reversals in relative position in pairwise comparisons between genotypes (e.g. 30–45% reversals when temperature was changed). They conclude, 'Thus, it is not possible to characterize one genotype as having a higher bristle number or faster development than another, since this can only be relative to a given environment' (Gupta

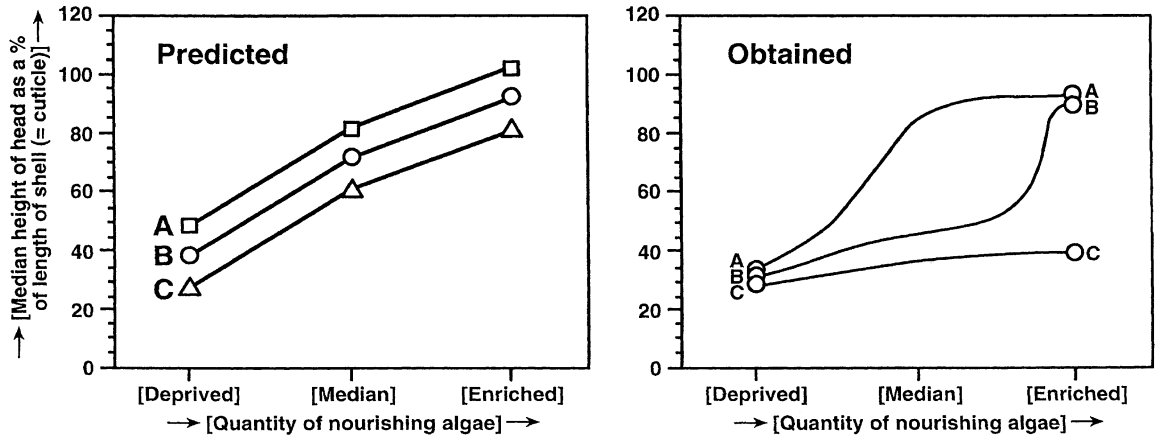

Figure 2 *Woltereck's interpretation of Johannsen's notion of the genotype's influence on phenotypic expression (predicted) and the actual results (obtained) of rearing three geographic varieties of* Hyalodaphnia cucullata *(females) on different levels of nourishment. (Translated and redrawn from Woltereck, 1909, Figs 11 and 12, pp. 138–139.)*

& Lewontin, 1982, p. 947). Their results contradict rather strongly the reaction-range concept, as well as the utility of the breakdown of phenotypic variance into independent hereditary and environmental components as gleaned from heritability estimates.

The limitations implied by the norm of reaction are best viewed as developmental, rather than strictly or solely genetic. The absence of strict predictability is now recognized in many quarters as a defining feature of development. It is specifically taken into account in such diverse formulations as dynamic systems theory (Thelen, 1990), individual-socioecological approaches (Valsiner, 2001), and developmental contextualism (Lerner, 2002).

As documented (Wahlsten, 1990), the calculation of heritability using the analysis of variance (ANOVA) is often insensitive to the statistical interaction of G and E because the detection of such interactions by that statistical procedure requires larger *N*s than are usually available in studies using humans.[1] The other weakness (not to say distortion) of relying on ANOVA-like statistics to determine the presence of a G–E interaction is the peculiar conclusion (for the statistically uninitiated) that obvious empirical interactions do not qualify as statistical interactions, such as the example in the left side of Figure 2. To clarify this point further, Figure 3 portrays three different forms of norms of reaction for phenotypes that vary quantitatively, such as height, weight, IQ, amount of extraversion, etc.

This hypothetical figure portrays the phenotypic outcomes of three genotypes studied over two environments. In the left panel, there is said to be no gene–environment interaction because the genotypes have maintained their ranking and the magnitude of the differences among them, resulting in parallel reaction norms. Obviously, this is a very specialized (sheerly statistical) use of the term interaction because the phenotype associated with each of the genotypes has changed from environment 1 to environment 2. The middle and right panels are said to be examples of gene–environment interaction because in the middle panel the reaction norms cross and in the right panel a phenotypic difference among them is brought out only in environment 2. While earlier we asserted that gene–environment interaction is the rule, in light of the above we will adopt the term gene–environment *coaction* to implicate the interconnectedness, if not the statistical interaction, of gene–environment interrelations as far as individual development is concerned.[2]

[1] As the next paragraph makes clear, the statistical concept of an interaction does not have the same meaning as the omnipresent notion of an interaction denoting a primary inseparability or interconnectedness of genes and environment, in the sense that all outcomes are the result of genes operating in a particular developmental milieu and that outcomes are likely to change when the developmental milieu changes. The statistical concept of interaction only recognizes certain changes as qualifying for the term interaction, as described in the next paragraph.

[2] In agreement with our premise, at the conclusion of his critique of the ANOVA and its use in behavioral genetics, Vreek (2000, p. 44) says: 'Behavior geneticists . . . should acknowledge that an analysis of variance is a statistical method that does not fit reality and should be judged against the background of the best material model we have of development, which is one of dynamics and interactions.' If the ANOVA is inadequate for getting at the development aspect of behavioral genetics, then it follows that it must not be an appropriate statistical tool for developmentally oriented social and biological science, where it is very widely used. It is clear that we desperately need a more developmentally adequate statistical method to replace the ANOVA. R.A. Fisher, himself the inventor of the analysis of variance, did not even approve of its use as a measure of heritability: '. . . one of those unfortunate short cuts, which have often emerged in biometry for lack of a more thorough analysis of the data' (Fisher, 1951, p. 217).

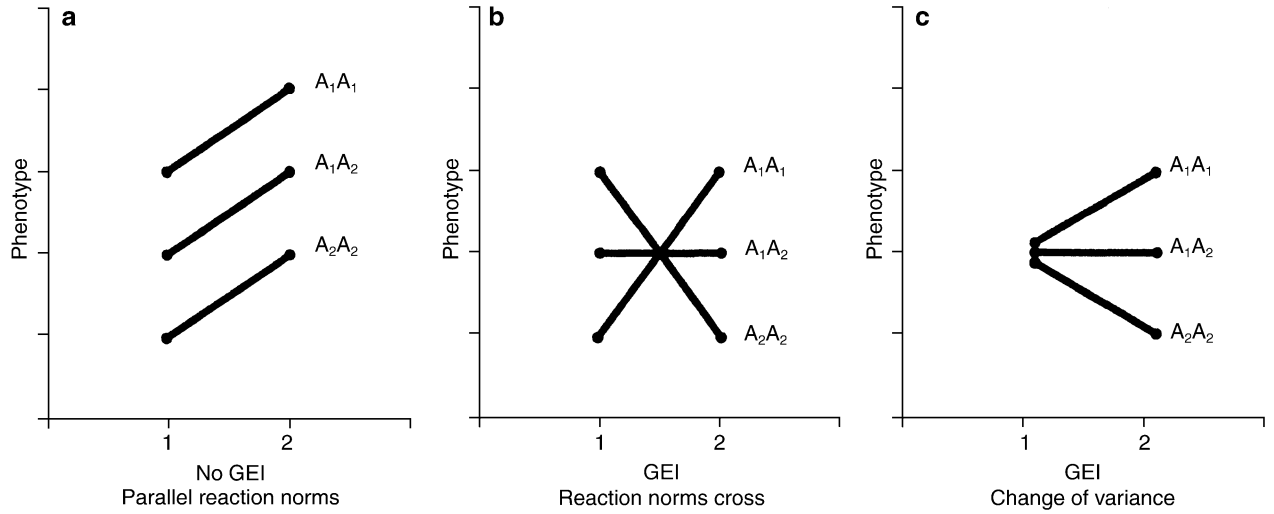

Figure 3 *a: Phenotypes are typically sensitive to changes in the environment. Here, the phenotypic value of each of three genotypes is plotted in two different environments (1 and 2). The environments can be the two sexes, social and physical environments (for example, diet, temperature), or alternative genotypes at a second genetic locus that affect the trait. The line joining the phenotypes of the same genotype in different environments is the norm of reaction of the genotype. Here, there are differences in the mean value of the quantitative trait between the two environments, but alternative genotypes react in the same manner to the change in mean. The rank order and absolute magnitude of the difference between the genotypes remains constant, and the norms of reaction are parallel. In this case, there is no statistical genotype-by-environment (GEI) interaction. b: Genotype-by-environment interactions occur when there is a change of rank order in the two environments. c: Interactions also occur when there is a change of variance with sex, environment, or genetic background. (Modified from Mackay, 2001; reproduced with the permission of the author and* Nature Reviews Genetics, *copyright Macmillan Magazines Ltd.)*

Norm of reaction vs. reaction range

The NOR holds that, if we know the phenotypic outcome of two genotypes under one rearing (environmental) condition, we cannot predict their relative standing when these genotypes (actually, organisms) are reared in a different environment. The reaction-range concept, on the other hand, '. . . presumes that the genotype imposes a priori limits (a range) on the expression of a phenotype' (Platt & Sanislow, 1988), such that the phenotype has upper and lower bounds that cannot be transcended. In Waddington's terms, the developing phenotype is genetically buffered or genetically canalized (Waddington, 1957, p. 36, Figure 5). This state of affairs is diagrammed in Figure 4. On the right side of the figure, the reaction ranges of the four genotypes are bracketed, as depicted by Gotttesman (1963).

It happens that there is an empirical study in the psychological literature that explicitly addresses the reaction-norm concept, a study by Cooper and Zubek (1958). The results very clearly support the reaction-norm concept. It is interesting to note that the study was carried out with the idea of a reaction range in mind, and that it is cited by Gottesman (1963, p. 273) as supporting the reaction-range concept. Cooper and Zubek reared maze-bright and maze-dull rats in either an enriched or a restricted environment and then tested them in a Hebb-Williams maze. Since they had the reaction-range concept in mind

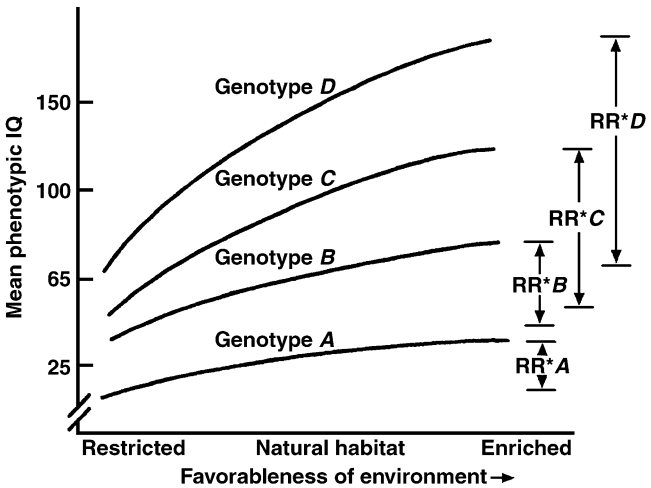

Figure 4 *Gottesman's schematic illustration of the reaction-range concept for four hypothesized genotypes. RR = Reaction range in phenotypic IQ. (From Gottesman, 1963, p. 255.)*

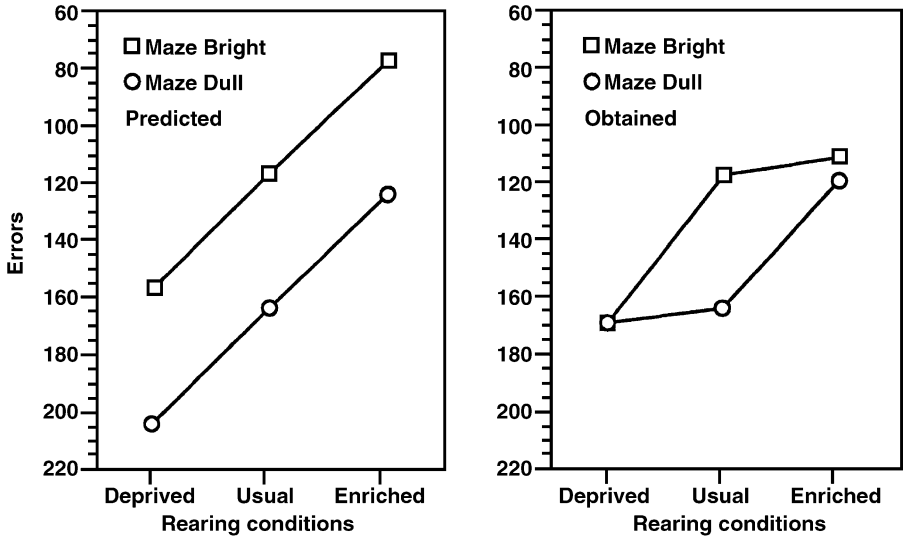

Figure 5 *Behavioral reaction range (predicted) and norm of reaction (obtained) for maze-bright and maze-dull rats' performance in a Hebb-Williams maze after rearing in three different environments. Obtained deprived and enriched data points are from Cooper and Zubek (1958); obtained usual data points are from Hughes and Zubek (1956). Only the obtained usual data points are significantly different from each other.*

in performing the experiments, they thought that the learning of both the bright and dull rats would improve relative to each other under the enriched rearing circumstances and would be poorer relative to each other when reared under the restricted (deprived) condition. (This prediction is illustrated on the left side of Figure 5.) Instead, as shown on the right side of Figure 5, they found equality of performance under both rearing conditions. The dull rats made as few errors as the bright rats after enriched rearing and the bright rats made as many errors as the dull rats after restricted rearing.

When the so-called bright and dull rats were tested in the Hebb-Williams maze after being reared in their usual way (neither enriched nor deprived), a significant difference between the strains appeared (middle points, right side of Figure 5). The reason is that this developmental situation repeats the rearing condition under which the original selective breeding for superior and inferior performance was carried out (Hughes & Zubek, 1956). If the reaction-range idea were correct and the genes coded for a range of learning ability (brackets on the right side of Gottesman's Figure 4), when these rat strains were reared under enriched or restricted conditions, the relative difference between them would be preserved. Instead, the experiment shows the genes are part of a developmental system or manifold. The highly specific consequences of rearing under a certain developmental condition were realized by selective breeding under that condition: The animals were selectively bred on the basis of their developmental reaction to that rearing condition. And, as called for by the norm-of-reaction concept, selective breeding under one developmental regimen does not predict outcomes under different rearing conditions. The results of selection depend on the entire developmental manifold, not only on the genes that are involved: To get stable outcomes, the developmental conditions have to remain the same from generation to generation (Gottlieb, 2002b).

A recent study by Kathryn Hood (2005) provides striking support for the developmental manifold idea in the continued dependence of the phenotypic outcome on the specifics of the rearing environment utilized as the basis for selective breeding. Hood and her colleague, Robert B. Cairns, were interested in selectively breeding mice for the expression of high and low levels of aggression. To this end, they placed animals in social isolation after weaning (such rearing enhances aggressive tendencies in some mice) and observed them in aggressive encounters around 4 weeks later. After only several generations of selective breeding based on the animals' response to isolation rearing in each generation, the high and low lines were clearly differentiated. Hood was interested in the question of gene–environment coaction, so after five generations of selective breeding, she raised one-half of each line in social conditions after weaning and examined their attack frequency in comparison to the other half of the lines reared in social isolation.

As can be seen in Figure 6, high line mice reared under social conditions ('group') were as non-aggressive as the low line, whereas the high line mice reared in

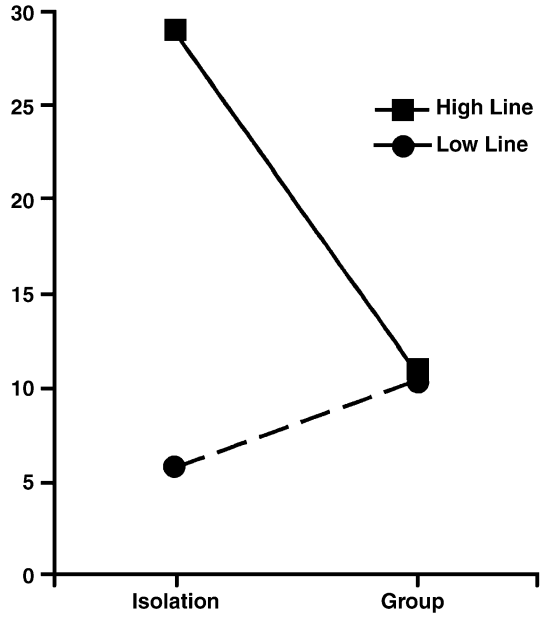

Figure 6 *After five generations of selective breeding for high and low aggression as a consequence of isolation rearing, Hood (2005) reared the two lines under social conditions ('group') and found no differences in aggressive behavior (i.e. the high line dropping to the level of the low line when socially reared). (Figure kindly supplied by K.E. Hood.)*

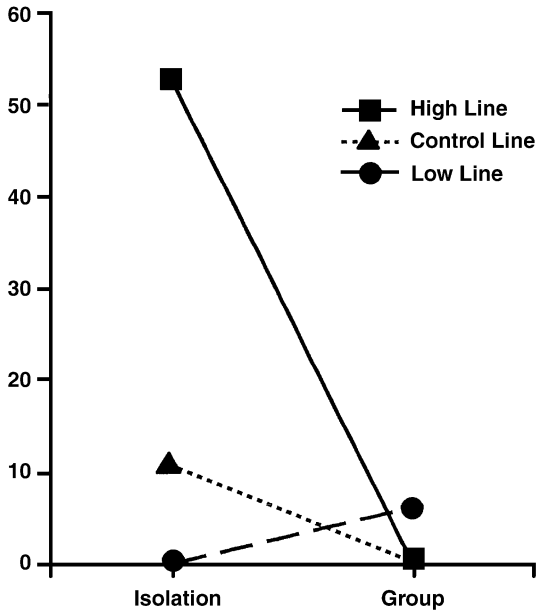

Figure 7 *After 39 generations of selective breeding for high and low aggression as a consequence of isolation rearing, Hood (2005) reared the two lines under social conditions ('group') and found no differences in aggressive behavior (i.e. the high line dropping to slightly below the level of the low line when socially reared). The control line is an unselected line. (Figure kindly supplied by K.E. Hood.) Further discussion in text.*

isolation continued to show a high level of aggressive attack behavior. A nice demonstration of developmental-relational causality or gene–environment coaction: The continued dependence of the selectively bred attack response on the rearing environment in which it was selectively bred. What may come as a surprise to some readers is that, after a further 34 generations of selection, the aggressive behavior of the high line is no less dependent on isolation rearing for its manifestation. As shown in Figure 7, the attack frequency of the high line drops to slightly below that of the low line when the mice are socially reared in the 39th generation. In Figure 7, the 500 line is an unselected line and their attack frequency is midway between the high and low lines when they are reared in isolation and drops to zero when they are reared socially, yet another example of gene–environment coaction, if we assume a genetic difference between the selected and unselected lines.

Behavioral development is not unique in its continued dependence on gene–environment coaction. Even under strong evolutionary selection pressure, morphological variation is similarly dependent (Griffiths, Owens, & Burke, 1999). Both the behavioral and morphological findings support the idea that understanding development requires a *relational* concept of causality: Development outcomes are a consequence of at least two specific components of coaction from the same or different levels of analysis (Gottlieb & Halpern, 2002). The basic notion here is that the emergent products of development are epigenetic, not just genetic, and this continues to be the case even when we are considering the evolutionary process.

A growing appreciation of this fact over the last several decades has fostered a renewed interest in development within evolutionary biology and increasing recognition that changes in evolution reflect changes in development. Contrary to the assumptive base of the neo-Darwinian synthesis of the last century, the introduction of phenotypic variation upon which natural selection acts is not strictly limited to random genetic mutation, drift, and recombination, but can result from a wide range of epigenetic processes contributing to individual ontogeny.

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