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Gene × Environment interaction: What exactly are we talking about?☆

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ABSTRACT

An ambiguity exists in how psychological scientists use the word "interaction." This word can refer to *physical* interactions between components that form the mechanisms in complex systems, but it can also refer to *statistical* interactions revealed by General Linear Statistical Models (e.g., Analyses of Variance). Statistical interactions indicate that the nature of the relationship between two variables depends on a third variable, but the discovery of such interactions does not constitute evidence of physical interactions between components in a system. Studies conducted using traditional behavioral genetics methods sometimes reveal statistical interactions between genes and environments, but the presence or absence of such interactions tell us surprisingly little about actual, physical interactions between genes and their contexts. This is important, because it is only the latter kinds of interactions that cause the development of behavioral phenotypes, including developmental disabilities. Therefore, when behavioral scientists discover (or fail to discover) Genotype × Environment interactions, it is important to exercise care in interpreting their meaning and in assessing the utility of such findings.

An old, unfunny joke in the scientific community tells the story of a person who comes upon a man searching under a streetlamp. When asked what he's looking for, the man replies that he has lost his keys. The passerby asks the man if he just happened to drop his keys while walking by this lamppost, but the man replies "No, I dropped them half a block down the street, but it's too dark down there to find *anything*, so I'm looking here." This story is understood to be a sort of parable about science: we tend to study phenomena about which we know something, even if the phenomena we're actually interested in are rather different, because if we know too little about what we are really interested in, it can seem virtually impossible to choose even the first step in our investigation.

In the late 19th century, Charles Darwin's cousin Francis Galton was stumbling around in the metaphorical dark, trying to figure out the first steps to take in teasing apart the relative contributions of Nature and Nurture to human characteristics (Galton, 1874, 1907). One of his most influential solutions was to study identical and fraternal twins. Generations of behavioral geneticists subsequently responded to the call to measure the characteristics of twins, and to use these measures to estimate the heritability of those characteristics (Moore, 2013a). Galton was remarkably insightful in some ways, and understood that these sorts of studies could yield interesting information. He was also a competent-enough mathematician that he was able to figure out how to measure the correlation between two variables (Galton, 1888). Given the ubiquity of correlation coefficients in contemporary science, it is hard to imagine that the tools required to study correlation had not yet been invented before Galton developed them for himself! We have Galton's interest in Nature and Nurture to thank for the statistical tool that allows us to evaluate the strength of the relationship

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between any two variables.

But to analyze the relationships between more than two variables—such as a genetic factor, an environmental factor, and a behavioral outcome—additional new techniques were required. To this end, Ronald Fisher, building on Galton's work, subsequently developed the Analysis of Variance (ANOVA) and the *F* statistic (named for Fisher) that an ANOVA yields. The ANOVA is a marvel of statistical insight, but it carries certain risks. Specifically, like the simpler correlational analyses that came before it, analyses of variance risk replacing concern for causal relationships, in which real events cause real outcomes, with concern for statistical relationships, in which two variables are mathematically related in ways that might or might not entail cause-effect relationships. In fact, early in the 20th century, Karl Pearson—the man Galton recruited to help him work out the mathematics of correlation, and for whom the Pearson product-moment correlation is named—went so far as to dismiss cause-effect relationships outright, calling "the category of cause and effect" a "fetish amidst the inscrutable arcana of even modern science," and a "conceptual limit to experience… without any basis in perception beyond a statistical approximation" (Pearson, 1911, p. *vi*). Following these developments in the early 20th century, "statisticians moved closer to mathematicians in ignoring the material world and dealing only with a world of forms, patterns, and associations" (M. Schield, personal communication, 28 May 2017). This is a specific case of the general problem of abstraction, wherein work with ideas replaces work with actual events in the concrete world.

1. Statistical interaction

Treatment of interactions as abstract, statistical phenomena is rooted in these century-old developments. Seven years after Fisher first used the word "variance" in its modern statistical sense (in a 1918 paper on the use of correlations to study Mendelian inheritance), he first used the word "interaction" in its modern statistical sense: "…we can find separately the variance between classes of type A and between classes of type B; the balance of the total variance may represent only the variance within each subclass, or there may be in addition an *interaction* of causes, so that a change in class of type A does not have the same effect in all B classes" (Fisher, 1934, p. 222, italics added). This is a kind of interaction with which most professional psychologists are familiar. If we look at the effect of two variables on a third variable—such as the effects of oven temperature and cooking time on the quality of a pizza being baked—we might find a statistical interaction such that the effect of cooking time *depends* on the oven temperature. Short cooking times can yield good pizza-crust outcomes in high-temperature ovens but undercooked dough (poor outcomes) in low-temperature ovens; long cooking times can yield good pizza-crust outcomes in lower-temperature ovens but burnt crusts (poor outcomes) in high-temperature ovens (a cartoon representation of these relationships is presented in Fig. 1, below). In Fisher's terms, a change in class of type A (cooking times) does not have the same kind of effect on outcomes in all B classes (oven temperatures), so statisticians say that cooking times and oven temperatures "interact" to determine the final quality of the pizza crust.

When translated into the analysis of variance associated with genetic and environmental factors, the logic is the same. In Fisher's sense, an interaction is revealed when the statistical effect of an environmental factor on a phenotype depends on the genotypes of the individuals in the population being studied; the environmental factor might appear to affect a population with one genotype in a different way than that same factor appears to affect a population with a different genotype. This information could potentially be useful, and many (if not most) of the examples of Gene × Environment (G × E) interaction discussed in this special issue of *Research in Developmental Disabilities* are likely examples of this type.

Perhaps the most well-known examples of this type of interaction were described in a series of papers by Caspi et al. in the first years of the 21st century (2002, 2003, 2005). In each case, empirical measurements revealed a significant statistical interaction between a genotypic factor and an environmental factor. For example, in seeking to account for variation in antisocial behavior, Caspi et al. (2002) reported a significant interaction between childhood experiences of maltreatment (none, probable, or severe) and variation in a DNA sequence used to build the monoamine oxidase A (MAOA) enzyme (high or low levels of MAOA activity). Likewise, in a study of depression, Caspi et al. (2003) reported a significant interaction between the number of stressful life events experienced (0, 1, 2, 3, or 4+) and variation in a DNA sequence involved in regulating production of serotonin transporters (high or

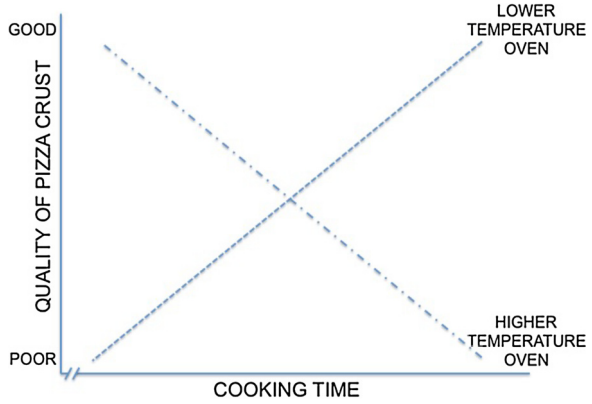

Fig. 1. Fictional representation of how oven temperature might interact statistically with cooking time to permit predictions about the quality of a hypothetical pizza crust.

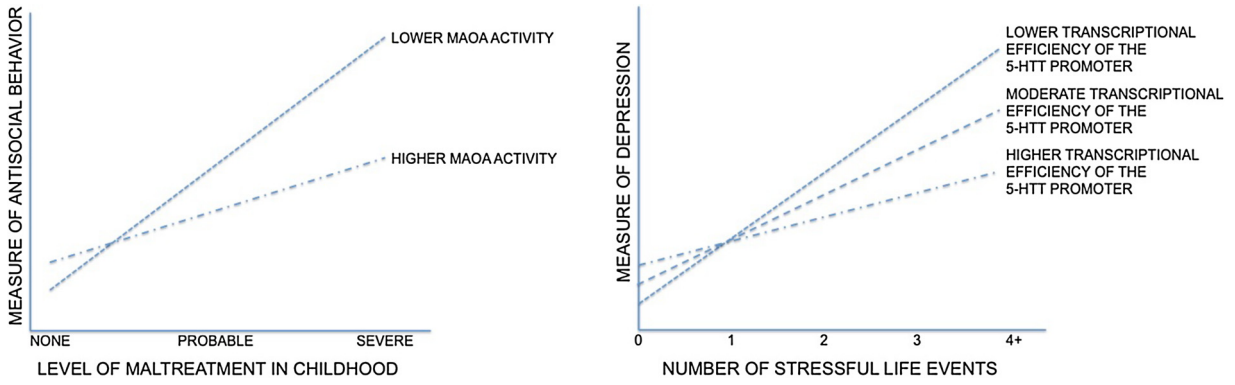

Fig. 2. Two figures adapted from articles published by Caspi et al. (2002, 2003). The left panel was adapted from Caspi et al. (2002), Figure 1. The right panel was adapted from Caspi et al. (2003), Figure 1D. Both figures have been redrawn, abstracting the statistical interactions reported in these papers.

low levels of transcriptional efficiency). In each case, the outcome—antisocial behavior or depression—was best predicted not by the genetic factor alone or by the environmental factor alone, but by the statistical interaction of these factors with one another (see Fig. 2, above).

The phenomenon of G × E interaction is extremely important; the presence of this special issue attests to the growing recognition of its significance. However, psychologists are at risk of underestimating the extent to which genuine, physical interactions between genes and environments are important in producing behavioral, cognitive, and affective characteristics. The tools developed by Galton, Pearson, and Fisher have contributed to the sense that gene-environment interactions can be studied by assessing the genotypes of individuals in a population, measuring some aspect of their developmental environments, and looking for relationships between these variables and the developmental outcomes of interest; in fact, this is the sort of approach adopted by Caspi et al. in their seminal work in this domain. And like the searcher looking for his keys under the streetlamp, this appears to be a reasonable plan of attack, because there is at least some prior work in this area that can light our way. However, the abstractions and words preferred by Fisher—which influenced virtually all subsequent studies that utilized traditional behavioral genetics techniques—have contributed to a conceptual confusion that continues to swirl around the idea of G × E interaction. In fact, the phenomena that are normally of interest lie elsewhere, under a streetlamp that is perhaps not as bright.

2. Physical interaction

At least since the 1950's, many developmental scientists have understood interaction differently than Fisher did. These scientists used the word "interaction" to refer to actual, *physical* interactions between components of developing organisms (e.g., Gottlieb, 1976, p. 219; Johnston, 1987; Lehrman, 1953, p. 345; Lickliter & Berry, 1990, p. 354; Waddington, 1968, pp. 9–10)). More recently, data from molecular biology have confirmed these developmental scientists' insight that all phenotypes—including normal and abnormal behavioral, cognitive, and affective phenotypes, just as much as biological phenotypes—emerge from physical interactions that take place during development, among components that comprise organisms (Blumberg, 2009; Edelman, 1992; Gilbert & Epel, 2015; Gottlieb, Wahlsten, & Lickliter, 1998; Johnston, 2010; Keller, 2010; Lewkowicz, 2011; Michel & Moore, 1995; Moore, 2002, 2013b; Noble, 2006; Stotz, 2006). For example, biological molecules like DNA change their activity levels as they physically interact with other molecules in their local environments. These molecules interact with DNA inside of cell nuclei, but in many cases, they originate in the broader environment outside of the organism (for example, in food or pheromones). The emerging sub-discipline of molecular biology known as epigenetics involves the study of these sorts of interactions (Moore, 2013a, 2015b, 2017). The kind of "interaction" Fisher had in mind—and the kind psychologists talk about when they report main effects and interactions after an ANOVA—is very different than the kind of physical interaction now known to characterize the emergence of phenotypes (and endophenotypes) in development.

To distinguish these two very different notions of "interaction," Griffiths and Tabery (2008) referred to the kinds of physical interactions that characterize development as "causal-mechanical" interactions. Specifically, they wrote:

> It is a truism that genes and the environment interact during the course of individual development. But … the standard behavioral genetic methodology for investigating relative contributions [of genetic and environmental variation to the total phenotypic variation associated with a trait in a particular population] is the statistical analysis of variance (ANOVA) … Notice that we have now introduced two concepts of interaction: (a) the causal-mechanical interaction between genes and the environment during individual development, and (b) the interaction between genotypic and environmental sources of variation in a population. [The developmental psychobiologist Gilbert] Gottlieb (2003) has emphasized the importance of recognizing the genetic and environmental relationship in a developmental—i.e., causal-mechanical—sense, stressing the idea of bidirectional gene-environment *co-action* in individual development (Griffiths & Tabery, 2008, p. 341).

As detailed further by Tabery (2014, 2015), the difference between Fisher's *statistical* sense of interaction and the molecular biologists' *causal-mechanical* sense of interaction has continued to sow confusion, as it has largely gone unrecognized by behavioral scientists who do not maintain a strict developmental perspective.

3. Statistical and physical interactions are strikingly different things

Perhaps the most significant problem that arises when the distinction between these two kinds of interaction is ignored is that the statistical results of traditional behavioral genetics studies can be misunderstood as revealing something about the developmental origins of a biological or behavioral characteristic. Because statistical interactions are discovered when one analyses data collected from *populations*, they tell us something about variation within those populations, but they tell us nothing at all about the causal-mechanical interactions that actually give rise to *individuals'* characteristics (Moore, 2008). As Griffiths and Tabery (2008, p. 335) wrote:

> Traditional, quantitative genetic methods are fundamentally unsuited to the study of the causal role of genes in development because they analyze and explain phenomena at the level of the population and not the individual organism, and because they explain the *differences* between individuals, rather than how those individuals came to have the phenotypes that they do (italics added; see also Ford & Lerner, 1992; Gottlieb, 1995, 2003).

By relying on Fisher's statistical abstractions, we wind up with information that does not bear any necessary relation to the real, physical phenomena that give rise to our individual characteristics during development. Unfortunately, studies of statistical interactions cannot illuminate the causal-mechanical interactions between genes and environments that actually bring phenotypes into being.[1]

To get a better feel for the marked difference between these two kinds of interactions, consider the following whimsical example, designed to illustrate the fact that statistical interactions can tell us very little about the causal-mechanical interactions that actually produce an outcome. Imagine you are a young scientist working in the U.S. in the early 20th century, and you are interested in what is responsible for some men going bald as they age. So you measure the density of hairs on a large population of young men's heads, and you continue to study these participants for the next 6 decades. When, as an octogenarian, you plot your hair-density data as a function of time, you would see the expected negative correlation: as the years pile up, the average hair density on the men's heads drops dramatically. But if you were interested in how a third variable might "interact" with time to "influence" hair loss, you could find yourself facing some strange results. Imagine, for example, that you decide to look at how hair loss is "influenced" by the distance of Halley's Comet from the sun (a silly example, to be sure, but remember, you're a scientist stumbling around in the metaphorical dark, so perhaps you have a theory that this could be a factor worth considering. Regardless of the absurdity of the example, it can reveal a deeper truth about statistical versus physical interactions).

Halley's Comet reached perihelion—the point in its orbit when it is closest to the sun—in 1910, whereupon it began moving further away until it reached aphelion in 1948, when it was as far from the sun as it got during that orbit. Then, it began its return trip toward its next perihelion, which occurred in 1986. If you plotted your hair-density data as a function of both comet-distance and era (e.g., 1910–1947 versus 1949–1986), you would find a classic cross-over interaction pattern (a cartoon representation of these relationships is presented in Fig. 3, below). Clearly, hair loss in your population was negatively correlated with the distance of Halley's Comet from the sun in the earlier era, because as the comet's distance increased, the number of hairs on men's heads decreased. But in the 38 years after 1948, hair loss was *positively* correlated with the distance of Halley's Comet from the sun; as the comet's distance from the sun decreased, so did the number of hairs on men's heads. So, the nature of the correlation *depends* on the era in which measurement is taking place: an archetypal statistical interaction. While this illustration shows the well-known disconnection between correlation and causation, it also shows how little connection there can be between *statistically* interacting variables and the *causal-mechanically* interacting system components that actually produce an outcome. Despite the statistical interaction represented in Fig. 3, is there any physical interaction between comet-distance-from-the-sun and era-of-measurement that is producing hair loss in adult men? Of course not.

4. Interpreting statistical G × E interactions

The understanding gleaned from this playful example must be applied when we try to make sense of the kinds of interactions we find in behavioral research on genes and environments, if that research does not actually study how physically interacting system components bring phenotypes into being. A statistically significant G × E interaction associated with a developmental disability—or any other phenotype—might not reveal *anything at all* about the developmental origins of that disability, because (as we saw in the Halley's Comet example) statistical interactions can exist among factors that are not the factors that physically interact to produce the outcome of interest. Given the non-experimental, correlational methods often used by behavioral scientists, a statistically significant

[1] Of course, it is possible to use subsequent experimental studies of molecular mechanisms to bolster inferences originally drawn from correlational (i.e., traditional) behavioral genetics studies. However, to date, most findings from traditional behavioral genetics studies have *not* been further explored with the goal of elucidating molecular mechanisms. And even if data from more mechanism-oriented fields can, in theory, help overcome gaps in knowledge left by correlational research, these data cannot overcome those gaps completely if they are drawn from studies of variation in *populations* rather than from studies involving *developmental* analysis of the mechanisms that cause phenotypes.

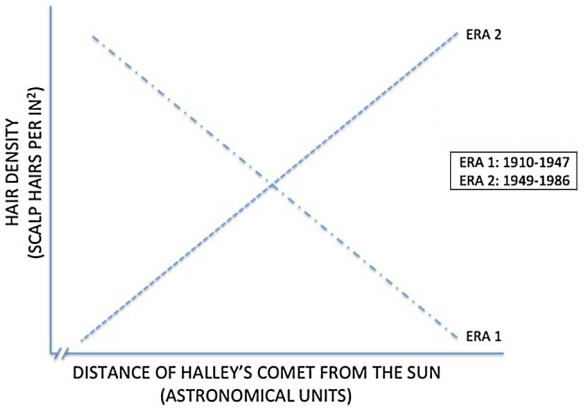

Fig. 3. Fictional representation of how era-of-measurement might interact statistically with the distance of Halley's Comet from the sun to permit predictions about scalp hair density in a hypothetical population of men.

G × E interaction cannot be taken to mean that the DNA segments or environmental factors being studied play a role in the development of the outcome being studied. They might, but they might not.[2]

The research findings of Caspi et al. (2002, 2003, 2005) can help us see how easily confusion can arise when we fail to distinguish statistical from physical interactions. When faced with the empirical finding that, for example, antisocial behavior is best accounted for by "interactions" between childhood maltreatment and MAOA activity, one might be tempted to conclude that antisocial behavior is the ultimate outcome when the DNA used to build MAOA physically interacts with biological molecules that are produced in the wake of maltreatment. In fact, such an inference was probably behind Caspi et al.'s (2002) claim that their findings "could inform the development of future pharmacological treatments" (p. 853). However, even though it is possible that antisocial behavior results from such physical interactions, it would be inappropriate to draw this conclusion without additional evidence. Given the non-experimental, correlational nature of this kind of work—in which genetic polymorphisms and experiential factors are simply measured, not manipulated—the causes of antisocial behavior might not have anything to do with physical interactions between MAOA genes and their environmental contexts. The principle underlying this conclusion is no different from the correlation-does-not-imply-causation verity that we learn in college, but it seems even easier to forget when we are thinking in domains involving multiple variables and the relatively unfamiliar terrain of molecular biology. Developing the most effective treatments for pathological conditions requires an understanding of the causal mechanisms responsible for those conditions, and although some studies of G × E interaction *appear* to give insights into those mechanisms, it is important to remember that they very well might do no such thing (for additional analysis of the meaning of Caspi et al.'s studies of G × E interaction, see Moore, 2015a).

The flip side of this situation is no less problematic. If a researcher *fails* to find a statistical interaction between the genetic and environmental factors under investigation, does that mean the behavioral phenotype in question does *not* depend on a physical gene-environment interaction for its development? No, it does not, because as always, null results are open to many possible interpretations. Just as the failure of a study to find a main effect of an environmental factor on a phenotype does not mean that factor plays no significant role in the development of that phenotype (Block, 1995; Moore, 2006), the failure to find a statistical G × E interaction does not mean the phenotype develops independently of physical interactions between the genetic and environmental factors being studied; the development of the phenotype still might depend on physical interactions between these factors. The reality is that even when the development of a phenotype depends critically on physical interactions between the specific DNA segments and environmental factors being studied, an ANOVA can fail to reveal a statistically significant interaction between those factors (for additional information about the interpretation of statistically insignificant G × E interactions, see Wahlsten, 1990). We can see the importance of this point by considering the fact that two large meta-analyses suggested that the findings published by Caspi and Moffitt's teams are not replicable (Munafò, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). Should we take the results of these meta-analyses to mean that the development of a major depressive disorder, for example, does *not* involve physical interactions between serotonin-related DNA and other biological factors that are affected by stressful life experiences? Such a conclusion is unwarranted at this juncture.

In fact, an overwhelming body of evidence from the biological sciences has made it clear that *all* phenotypes—including abnormal phenotypes like those that characterize developmental disabilities—emerge during development as a result of causal-mechanical interactions between genetic and non-genetic factors (Blumberg, 2009; Edelman, 1992; Gilbert & Epel, 2015; Gottlieb et al., 1998; Johnston, 2010; Keller, 2010; Lewkowicz, 2011; Michel & Moore, 1995; Moore, 2002, 2013b; Noble, 2006; Stotz, 2006).

[2] Note that the argument here is about non-experimental research methods in general rather than merely about the choice to conduct correlational statistical analyses. Imagine we collect data for a study in which we measure—but do not manipulate—two nominal variables (e.g., sex and city-of-birth). We might choose to analyze these data with an ANOVA rather than a correlational analysis, but regardless of that choice, the data remain correlational (in the sense of "non-experimental") because they cannot be used to make valid causal inferences. The problem being described here is related to methodology rather than to choice of data-analytic strategies.

Consequently, any conclusion that a phenotype is caused only by genetic and/or environmental factors *working independently from one another* is erroneous, even if a statistical analysis has revealed main effects of genes and/or environments, but no G × E interaction. Importantly, drawing mistaken conclusions from such analyses could have a variety of negative consequences, including leading researchers to prematurely abandon studies of certain genes or certain environmental factors, or in some cases, leading the general public to assume that some phenotypes are genetically determined and immutable, even though that is not actually the case. (Although a further discussion of this point is beyond the scope of the current paper, additional information is available in Moore, 2013b, 2015b.)

5. Understanding development in a useful way requires a focus on causal-mechanical interactions

Usually, when researchers report G × E interactions related to developmental disabilities, *we have absolutely no idea if those disabilities were or were not influenced by any actual physical interactions between the genes that were studied and the environmental factors (or their biological proxies) that were measured*. This might not matter if the goal is merely to make predictions *and* if a statistically significant interaction has been detected, because if both of these conditions hold true, one could place a good bet that a developmentally disabled person with one genotype might respond well to a particular treatment whereas a developmentally disabled person with a different genotype might not respond well to that same treatment.[3] There is obviously some value in discoveries of this sort, as they hold out the promise of individualized diagnosis and treatment. But such interactions will not help us understand the *development* of the disability, and will not lead us to other potential treatments—some of which could be more effective, less expensive, and/or easier to implement—because the mechanistic causes of the disability will remain shrouded in mystery. In contrast, developmental studies of the physical interactions that actually cause phenotypes normally illuminate several possible points-of-intervention in phenotype-producing developmental cascades, any of which might be targets of effective treatments (for detailed presentations of this important argument, see Moore, 2002, 2015a).

The call for submissions to this special issue noted correctly that “during development, the interaction between genotype and environment … is paramount to the ontogeny of the specific phenotype…” However, the call for submissions then pointed out that work on G × E in psychiatry “[has not yet reached] the point of being able to inform individualized diagnosis and treatment,” perhaps because “conclusive indications of causal G × E patterns are largely lacking in the field.” These statements are true, but they seem to suggest that standard analysis-of-variance-style approaches potentially *could* yield indications of causal G × E patterns, *even though the non-experimental, correlational nature of the kinds of G × E studies that have traditionally characterized psychiatric research (i.e., traditional behavioral genetics studies) does not permit conclusive revelations about causal-mechanical G × E interactions*. A subsequent statement in the call for submissions rendered a service to our field by emphasizing “the need to take into account a multilevel approach, one that combines genetic, environmental, epigenetic, neural, and hormonal perspectives, to better understand the mechanisms[,] the ontogeny[,] and outcome of different developmental disabilities.” However, it will be important to remain cognizant of the limitations of non-experimental, correlational, behavioral-genetics-style approaches to discovering G × E “interactions,” because such approaches often inadvertently obscure the nature of the causal-mechanical interactions that actually bring developmental disabilities into being. Researchers interested in making discoveries that have the potential to yield effective treatments for such disabilities would be best served by remaining focused on the mechanisms that cause phenotypes to develop.

Ultimately, we welcome any discoveries that improve the lives of individuals at risk for developmental disabilities. And discoveries of statistical G × E interactions have the potential to yield customized treatment programs that can help more individuals than can one-size-fits-all programs. However, we ought not imagine that such discoveries reveal anything about the mechanical interactions between genes and their environments that give rise to disabilities in development, or that better treatments would not be realized by investigations of those mechanical interactions. Likewise, we ought not imagine that if we *fail* to discover a statistical G × E interaction, the developmental disability being studied must be caused either by genetic or environmental factors working independently of one another. The data of molecular biology suggest otherwise; *all* phenotypes emerge in development from causal-mechanical gene-environment interactions. If our studies do not reveal these interactions, it is surely because we are searching under the wrong lamppost.

Conflicts of interest

The author declares that he has no conflicts of interest.

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[3] It is worth remembering that even in such circumstances, perfect prediction cannot be expected, because some individuals with both a genetic risk factor and an environmental risk factor might not develop the disability, whereas some individuals who have neither risk factor might still develop the disability. Many thanks to George F. Michel for bringing this point to my attention.

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