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Commentary: Gene by environment interplay and psychopathology – in search of a paradigm

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The articles in this Special Issue (SI) extend research on G×E in multiple ways, showing the growing importance of specifying kinds of G×E models (e.g., bioecological, susceptibility, stress-diathesis), incorporation of sophisticated ways of measuring types of G×E correlations (*r*GE), checking effects of statistical artifact, exemplifying an impressive range of quantitative and biological methodologies, and pointing to clearly needed next-step studies such as summarizing across many genes in gene sets (*Bentley et al.*¹) or in genome-wide pathway based approaches to G×E (*Winham & Biernacka*) and prediction of clinical outcomes (*Rapee et al.*). As a group, they document nicely that gene × environment research has come of age. What is the import of this? Does it represent a major new development in our field, or merely an incremental change of a framework that remains fundamentally unchanged?

Clinical psychopathology research is generally seen as pre-paradigmatic²—it lacks a unifying framework such as that of evolution that organizes biology. If psychopathology research had an integrative framework—I would not reach to call it a paradigm—it was the diathesis-stress idea (Meehl, 1962; Zubin & Spring, 1977); for a classic analysis see Monroe and Simons (1991); for a contemporary critique that emphasizes the form of the interaction beyond formal diathesis-stress into plasticity, see Belsky and Pluess (2009). A valuable, related but distinct formulation was outlined in the bioecological model (Bronfenbrenner & Ceci, 1994), which foreshadows much of today's work and is also noted in several of the papers in this special issue. Putting it crudely, the fundamental idea has been that psychopathology arose from the combination of an unspecified constitutional (read: genetic) liability that, when combined with unspecified stressor or insult, leads to deviant development. While this idea was often fruitfully used, it suffered from some fundamental problems that prevented it from really organizing work in the field. One problem was that it was vague—what genetic liability? How would this be measured or specified? Which experiences (Monroe & Simons, 1991)? The second problem was the difficulty of testing

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¹Articles in this issue (with italicised author names on first mention) can be found at <http://onlinelibrary.wiley.com/doi/10.1111/jcpp.12134>.

²A formal philosophy of science would challenge the use of paradigm in this context, but I use the term here heuristically to mean a perspective that might be shared by the entire field and help its knowledge become cumulative.

this fundamentally interactive model mathematically—a problem still being worked on (Belsky et al.).

The result was that most psychopathology research has emphasized main effects. These could be main effects of adverse environments, such as abuse, poverty, prenatal health, or neglectful or overly harsh parenting. Alternatively, they could be main effects of heritability or of specific genes. Enough significant, though generally disappointingly small, effects were found over the years that the operating paradigm was not really diathesis $\times$ stress, but main effects.

Over the past 15 years, fundamental changes in available technology have created a new opportunity for the field to operationalize a dynamic conception of developmental psychopathology. Molecular genomics has become widespread and affordable: candidate genes can be assayed by virtually any serious researcher, and numerous centers now have the ability to access genome wide arrays, expression arrays, or large enough twin samples to examine interactions with measured environments. On the horizon may be targeted sequencing (e.g., exome sequencing or other modified approaches) that are affordable to a significant number of research teams thanks to the transition from Sanger-based to “second generation” genome sequencing, such that initiatives for large scale whole-genomic sequencing of large samples are in the offing. While the informatics challenges of sequenced data sets have yet to be resolved, there can be little doubt that powerful new information about the genomic correlates of psychopathology will continue to emerge, probably at an accelerating rate, in the coming decade. In a sense, genomics is about to come of age as well.

Moreover, environmental and experiential studies have become more sophisticated. Multiple time--point measures, longitudinal studies, computerized measurements, greater computer power enabling modeling of more sophisticated statistical models, and more detailed mapping of psycho-biological pathways of experience in relation to stress resilience, allostatic load, family process, and culture have all improved our grasp of the experiential inputs throughout development that are correlated with, and potentially play a causative role in or moderate, psychopathology. It is important not to over-simplify the challenges of integrating environmental inputs—they are often correlated, they may act synergistically, and the mechanisms through which they work are able to be elaborated at volume length. Extensive, sophisticated models of how stress or experience works psychologically and biologically cannot be reduced to a simple ‘G $\times$ E’ statement without considerable qualification. Yet in spite of, or perhaps because of, this sophistication, enriched models of environment and its interplay with genes are now informed by detailed mechanistic ideas that create increased potential for fruitful cross-talk between often-separate lines of inquiry into gene and environmental mechanisms.

In the past decade, the opportunity has been articulated explicitly in terms of gene $\times$ environment interplay (Rutter, Moffitt, & Caspi, 2006). Now some specificity may be able to fill in the details of either diathesis $\times$ stress, plasticity $\times$ experience, or the bioecological model. Perhaps we have the possibility of a tractable and potentially paradigmatic approach to developmental psychopathology research that goes beyond a generic ecological or

interactive model to a specific process account. Perhaps most attractive of all is the potential, if such a ‘paradigm’ were to succeed, of direct clinical applicability via personalized medicine approaches at some point in the future for mental illness and health (*Campbell et al.*), assuming future ethical issues are resolved.

Thus, the sweeping breadth and impressive sophistication of the collection presented here does raise the interesting question: does G×E represent a potential organizing paradigm for psychopathology research that is now coming of age and allows meaningful updating of the classic but under-utilized attempts at organizing paradigm?

Several objections remain to drawing such a lofty conclusion about paradigms. For example, some might argue that G×E is not really a paradigm but an analytic or methodological approach; that specific G and specific E are still at a fairly primitive level of analysis compared to what will be needed to really imagine personalized medicine or personalized prevention programs for mental health; that some crucial research questions do not lend themselves to G×E logic; and so on. One could counter these arguments with more advanced mechanistic models of G×E processes that are conceptual and related to biology (e.g., Belsky & Pluess, 2009), but we would probably not yet reach consensus as to whether we have a paradigm.

However, we may be moving in that direction rapidly. I highlight two particular elements that constitute opportunities to increase the organizing and paradigmatic potential of a G×E perspective for psychopathology. These two elements are related: (a) causality (*Harold et al.*) and (b) biological mechanism (*Lewis et al.* touches on both points). I begin with the second.

An attractive and sometimes neglected feature of claiming G×E as quasi-paradigmatic is that it can be approached both conceptually and methodologically at the level of biological mechanisms. Consider the phenomena of epigenetic modification as a mechanism in psychopathology. DNA methylation, to take one example of epigenetic mechanism, can be altered by psychopathology risk factors such as maternal stress (*Sng & Meaney, 2009*), prenatal or postnatal toxicant exposure (*Bailey et al., 2013*), prenatal diet (*Drake et al., 2012*), and perhaps other events. It is unlikely that the brain does not participate in such effects, and a few studies have begun to link behavior to epigenetic change and to gene expression (see *Bartlett et al.*). It is likely that these epigenetic phenomena also interact with DNA structure (genetic × epigenetic interaction) such that only some genotypes undergo epigenetic change in the presence of a given environmental risk or event.

Thus we can ask, is developmental psychopathology an epigenetic phenomenon? Are ADHD, autism, and other developmental conditions epigenetic diseases? If so, what is their molecular mechanism at the epigenetic level? What experiences, what genetic (DNA) assignments, and what specific epigenetic alterations at what point in development, are shaping the probability of emergent psychopathology? These broad and ambitious questions are rapidly moving from the imaginary to the tractable, and they fall within a G×E “paradigm” of a conceptual model or paradigm of how psychopathology emerges and how it

should be studied. Indeed, we probably need to describe these mechanisms before we will truly have a paradigm in the traditional sense of the word to describe scientific paradigm.

The full causal picture of course remains still more complex—gene-environment correlations, genetic influence on environmental or experiential events, and related feedback mechanisms all complicate our causal story as carefully noted by some of the current group of contributors. It will not be a simple linear story. That said, some causal inferences can also be made if we adopt causally informative designs to go along with our G×E experiments (Lewis et al.). For example, studies of sibling pairs in which only one of the siblings was exposed to an environmental influence enable some degree of causal inference (D’Onofrio, Van Hulle, Goodnight, Rathouz, & Lahey, 2012); these could be combined with genetic and epigenetic analyses to gain purchase on direct molecular mechanisms of causal influence. Such studies are waiting to be done. Even in correlational designs, in which strict demonstration of causality is not possible, some estimate of potential for causal effects can be made via statistical means (e.g., probability weighting, propensity score matching) and enhanced by biological measures. And in the case of intervention (stress reduction, dietary improvement), a randomized causal design can be employed even in human studies, combining a prevention trial with genetic and epigenetic analyses to evaluate G×E effects in a causal context that refutes or supports an hypothesis developed by a correlational study.

It has been the case for some time that most genetic studies can be enriched by including some measures of environment (difficult but not impossible in the large, pooled data sets being assembled for this purpose), and that studies of environment and of treatment generally benefit from including genetic data (possible even in smaller studies of a targeted rather than whole-genome approach is taken, and if specific hypotheses of mechanism are tested). But an explicit unification of these traditionally disparate approaches is needed, and should be reachable, by formalizing the understanding that G×E is a guiding framework, perhaps informed by emerging epigenetic mechanisms. The challenge will be to specify how the components overlap or differentiate for particular forms of psychopathology. Whether we can reach a general model, or whether we will require distinct sub-models, remains to be seen. The amount of work still to do is extensive—we know little about human epigenetic change or about developmental timing of effects, and genetic and environmental measurement both have much growing and integrating still to do. However, we can look forward with interest to the upcoming period of research in this area and consider the intriguing possibility of this field reaching something like a paradigmatic phase.

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