

Towards a Truly Developmental Epigenetics

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Abstract

Conceptual and empirical advances across the biological and psychological sciences have made it increasingly clear that genetic and environmental factors cannot be meaningfully partitioned when attempting to explain development. This should be a major theme within the contemporary field of epigenetics. However, the field has yet to fully extricate itself from reductionist tendencies in its conceptualization of developmental relations. Epigenetics today still routinely promotes both a reductionist privileging of molecular over molar levels of explanation and a reductionist focus on separate and distinct roles for genes and environment in any given developmental relation. We argue that the field needs to more rigorously pursue a process-oriented framework that is integrated across molecular, organismal, and environmental levels of biological organization. Transcending the worn and outdated nature-nurture controversy will require a truly *developmental epigenetics* that embraces the importance of emergence, context, and hierarchical relations in all developmental explanation. © 2017 S. Karger AG, Basel

The articles of this special issue attest to the fact that the term *epigenetics* has a variety of meanings, interpretations, and implications for the study of human development. For example, in developmental biology, the term *epigenetic* emphasizes the context dependence of developmental processes; in genetics, epigenetics refers to “mechanisms” (in the mechanistic sense) of gene regulation that do not require changes in DNA sequence; in evolutionary biology, epigenetics implies non-DNA-based mechanisms of inheritance, and in population genetics, epigenetics provides examples of phenotypic variation in response to environmental conditions [Müller &

Olsson, 2003]. Although these examples highlight the different questions and concerns evident at different levels of analysis across biological disciplines, all touch on the necessary interplay between “nature” and “nurture” in the generation of both developmental and evolutionary change. The key question facing contributors to this special issue is whether or not epigenetics’ relational focus moves beyond reductionist, variation-partitioning views of developmental “interaction” (or “relations,” as we shall hereafter substitute, in accordance with Lerner and Overton’s suggestion in this issue) to embrace a truly holistic, process-oriented approach to developmental relations, one that legitimately transcends the trappings of the nature-nurture debate.

Nobody today would deny that phenotypic outcomes are the result of complex and dynamic relations among genotype, developmental processes, and environment. At this point, most biologists and psychologists also agree that it is not possible to directly deduce or predict phenotype from genotype. Indeed, this fact has been recognized for decades. Nearly 50 years ago, Gottlieb [1970] pointed out that all development is necessarily probabilistic rather than predetermined, as traits and characteristics emerge during development from real-time coactions that occur among factors operating at multiple levels of analysis, from genes to neural activity, from cells to organs and bodies. The probabilistic nature of development yields a critical insight: simply put, developmental outcomes cannot be prespecified *in any form or manner* by factors that are present prior to the process of development. This insight is fundamental to contemporary developmental science and to a holistic view of developmental relations. However, it continues to be overlooked or misunderstood in some quarters of biology and psychology.

This is the case, in large part at least, because of the history of thinking about the genotype/phenotype distinction going back more than a century (the distinction was originally proposed by Johannsen in 1909 [see Johannsen, 1911]). In the predominantly gene-centered view of 20th century biology, the relationship between genotype and phenotype was essentially a relationship between cause and effect, between “a plan and a product” [Jablonka & Lamb, 2005, p. 33]. This genocentric framework can be traced most directly to the work of the German biologist August Weismann (1834–1914), one of the founders of what came to be the field of genetics. His “germ plasm” theory of development was based on a distinction between those phenotypic traits or characters that were intrinsic to the organism and those that were the result of the effects of experience with the environment. This distinction assumed that some phenotypic outcomes could be prespecified in the germ plasm itself, independently of environmental factors and already determined at conception. By Weismann’s view, the germ plasm was fully insulated from environmental or developmental influences and therefore could pass unchanged to the next generation.

Weismann’s view set the biological sciences on a course that increasingly separated the organism from its environment, thereby fueling a reductionist conceptualization of relations between the “forces” of nature and those of nurture that powerfully influenced thinking about both development and evolution for much of the 20th century. As Overton [2006] noted:

The controversy [of the nature/nurture debate] is supported by the neo-Darwinian radical rupture of the whole into an inside (gene, biology) story that comes to be called nature, and an outside (social-cultural, experience) story called nurture ... the controversy becomes questions of which one fundamentally determines change, or how much does each contribute independently to determining change. (p. 43)

In this framework, relations between genetic and environmental factors were seen to be one way – genes could determine the possible contributions of the environment and could specify when and how the environment had its effects, but experience with the environment could not have a comparable effect on genes [see Johnston, 2009, for further discussion].

Weismann's view of phenotypic development was also widely embraced in 20th century psychology [Lickliter & Honeycutt, 2015], resulting, at times, in sharp distinctions between innate (instinctive) and acquired (learned) behavior in the first half of the last century [Logan & Johnston, 2007]. Such a framework contributed to the growth of several related fields, including sociobiology, behavioral genetics, cognitive science, and evolutionary psychology in the second half of the last century. However, as Lerner and Overton [this issue] systematically articulate, this dichotomous way of thinking is no longer biologically tenable. Evidence that genes are not insulated from environmental influence has been accumulating for half a century. Beginning in the late 1960s, evidence began to emerge that gene transcription could be affected by an organism's environmental experience [e.g., Rose, 1967; Uphouse & Bonner, 1975], an idea that was completely inconsistent with the widely embraced Weismannian view of phenotypic development. Over the last several decades, a wealth of findings drawn from epigenetic research has indicated that genetic *and* nongenetic factors constitute a dynamic, mutually dependent, relational developmental system within which the various levels and components of the system coact to promote the emergence, maintenance, or modification of phenotypic traits [Gottlieb, 1998; Moore, 2015].

Conceptual and empirical advances across the biological and psychological sciences have made it increasingly clear that genetic and environmental factors cannot be meaningfully partitioned when attempting to explain development. This should be a major take-home message of contemporary epigenetics [Lickliter, 2009]. However, as contributors to this special issue have made clear, the discipline has yet to fully extricate itself from reductionist tendencies in its conceptualization of developmental relations. Yes, epigenetics has significantly contributed to newfound appreciation within the biological and psychological sciences for the “interdependence of organism and environment” and for the “instructive role” that extragenetic, environmental factors play in phenotype construction [Stotz & Griffiths, 2016, p. 22], repudiating Weismann's genocentric focus in the process. Nonetheless, conceptualizations of development within contemporary epigenetics still routinely trade in *both* a reductionist privileging of molecular over molar levels of explanation *and* in a continued reductionist focus on separate and distinct roles for genes and environment in any given developmental relation. We turn now to an elaboration of each of these reductionist tendencies – tendencies that significantly undermine the conceptual potential of epigenetics for moving beyond “weak” [Lerner, 2002], “middle-ground” [Allen & Bickhard, 2013; Spencer et al., 2009], and “variation-partitioning” [Tabery, 2014] approaches to developmental relations.

The Explanatory Molecularization of Developmental Relations

Arguably, the signature contribution of contemporary epigenetics is its molecularization of the nurture side of nature-nurture relations [Griffiths & Stotz, 2013]. By establishing molecular “analogues” for an organism's experience with the world in

the form of histone proteins and methyl groups, epigenetics holds out promise for understanding “the ways in which social structures and socio-economic differences literally get *under the skin (and in the brain)*” [Meloni, 2014, p. 6; see also Robert, this issue]. Such promise, however, can potentially encourage a reductionist view of epigenetic molecular factors as *the causal embodiment* of an organism’s transaction with the world, on the assumption that these molecular factors effectively “translate” organismic experience into a direct relation with the genome [Meloni, 2014]. Such promise, in other words, can inspire new forms of deterministic thinking that are wholly inconsistent with a holistic view of the developmental process. As Moore [this issue] persuasively argues,

Rather than challenging the idea that there are biological molecules that single-handedly cause phenotypic outcomes, this focus could reinforce that very idea; in this case, research on epigenetics could simply shift attention from one kind of molecule, such as DNA and the “code” it carries, to other kinds of molecules, such as histone proteins and the putative codes they carry. (p. 73)

To the extent that causal status is conceptually assigned to the molecular *relations* between genetic and epigenetic factors, rather than to the factors themselves, the field of epigenetics can effectively avoid the kind of “epigenetic” deterministic thinking against which Moore cogently warns. But in its identification with the molecular, contemporary epigenetics conceptually reinforces the idea that analysis at the molecular level of process is somehow necessary to confer legitimacy on organism-environment transactions – that analysis at the molar level of process offers little to no explanatory value in its own right until it is translated into “real mechanisms” at the molecular level of analysis. This, in turn, revitalizes the centrality of the genetic level of analysis. Although contemporary epigenetics has denuded genes themselves of all-encompassing formative prowess by highlighting epigenetic factors of influence, it has ironically reinforced the notion that what happens at the genetic level of analysis is explanatorily foundational through its very focus on the molecularization of epigenetic processes.

Saunders [this issue] notes that a surprising amount of contemporary epigenetics is still primarily gene focused, committed to a narrow meaning of epigenetics as the molecular processes that can modify gene activation states to be inherited without change in DNA sequence. As Saunders points out [this issue], this molecular approach goes back more than half a century [Nanney, 1958], when epigenetics was framed as the problem of how to account for gene’s differential activation. Waggoner and Uller [2015] argue that this emphasis on genes and their activation has resulted in various forms of “epigenetic determinism” [see also Moore, this issue], in which epigenetic research remains committed to reductionistic notions of the genetic control of phenotypic outcomes. Saunders goes on to propose that the evidence available from work in epigenetics could lead to a paradigm shift in terms of both development and evolution, but this will occur only if the definition of epigenetics is broadened beyond the molecular level and refocused on the whole organism rather than just the gene.

In this light, David Crews and his colleagues have argued that it is useful (and necessary) to differentiate two forms of epigenetics, *molecular* and *molar*, or “bottom up” versus “top down” epigenetics [e.g., Burggren & Crews, 2014; Crews, 2008, 2010]. Whereas the focus of molecular epigenetics is primarily transcriptional and translation control of gene activation, the focus of molar epigenetics is the individual organ-

ism's transactions with its physical, biological, and social environments through time. Crews and colleagues point out that it is still common to assume that the study of epigenetic processes can only be conducted at the level of the genes. In much of the field, epigenetics simply refers to the relations between genes, with transcribed portions of the genome, and between the products of both [Percival & Richtsmeir, 2011]. Crews and colleagues propose that a fully realized approach to epigenetics must encompass both the processes at play at the molecular level as well as those at the level of both the individual organism and the evolution of the population [Burggren & Crews, 2014; Crews & Gore, 2014; see also Hallgrimsson & Hall, 2011 for a similar argument]. Crews [2010] notes that:

Molar and molecular epigenetic modifications interact. Thus, changes at various levels (e.g., pattern of gene expression, physiological systems, and the organization and activation of brain circuits) bring about functional differences in brain and behavior that result in molar epigenetic changes. These then modify how individuals respond to conspecifics and their environment, bringing about changes at higher levels of biological organization. (p. 394)

In keeping with this expanded approach, a growing number of investigators are broadening the focus of their research attention to include not only internal factors (genes, proteins, cells, hormones) at play in phenotypic development, but also the contributions of the varied physical, biological, and social resources available to an organism in its developmental context [i.e., Gilbert, 2005; Gilbert & Epel, 2009; Moczek, 2015]. This approach has provided convincing evidence that developmental outcomes simply cannot be prescribed at the molecular level of analysis – the course of development emerges from the regulatory dynamics of the gene-in-a-cell-in-an-organism-in-an-environment system [Lickliter & Honeycutt, 2015; Oyama, 1985; Robert, 2004]. From this perspective, epigenetics is best viewed as the integration of processes at the molecular, organismal, and environmental levels of biological organization [Hall, 2011].

The work of Cole and colleagues [Cole, 2014; Cole et al., 2007; Slavich & Cole, 2013] illustrates this key insight by providing evidence of the rich interplay between biological and social levels of analysis. Cole and his collaborators identified 209 genes that were differently activated in circulating leukocytes from individuals reporting high versus low levels of subjective social isolation. These genes included those known to be involved in immune activation, transcription control, and cell proliferation. For example, impaired transcription of genes associated with glucocorticoid response and increased proinflammatory transcription pathways were identified in socially isolated individuals, suggesting that genome-wide transcription activity can be altered in individuals experiencing high levels of subjective social isolation [Cole et al., 2007]. As Robert [this issue] argues: “We are both and simultaneously biological and social creatures, and our research strategies must honestly capture this dual nature if they are ever to be adequate to and for us” (p. 99).

Although calls within the field for broadening the study of epigenetics well beyond the molecular processes involved in gene activation are becoming increasingly prominent [e.g., Hallgrimsson & Hall, 2011; Larsen & Atallah, 2011; Moore, 2015], epigenetics, as a discipline, has yet to uniformly eschew the widespread explanatory privilege that is granted to molecular – relative to more molar – levels of analysis. As a result, epigenetics does not currently deliver a framework conceptually coherent enough to transcend the trappings of the nature-nurture debate. Even more trou-

bling are the decidedly reductionist leanings within the field that all too commonly attach to conceptualizations of developmental relations *at any level of analysis*, from the molecular to the molar. From our view, it is within the conceptualization of developmental relations themselves that epigenetics most significantly fails to embrace the kind of holistic process orientation necessary to overcome the nature-nurture debate.

The Mechanistic Decomposition of Developmental Relations

Thanks to the historical tradition of partitioning environmental and genetic contributions to development over the last century, there remains a strong undercurrent of opinion in epigenetic research that the role of genes and environment can somehow be considered different and separable. Moore [this issue] draws attention to the long-standing influence of statistical approaches to interaction – especially prominent in disciplines like behavioral genetics – wherein the relation between genetic and nongenetic factors in phenotype construction is conceptualized in terms of how much variance in a population can be accounted for by each factor independently (i.e., through main effects) as well as in combination (i.e., through interaction effects). As Moore points out, framing developmental relations in terms of these statistical approaches significantly undermines what it means to establish genuine “mechanistic explanations of phenotype development” (p. 75), given that partitioning variance in terms of main effects and interactions is wholly inappropriate and grossly misleading when applied to the explanation of *individual development* [Gottlieb, 2003; Moore, 2013].

Moore [this issue] cautions proponents of epigenetics research against the conceptual pitfalls of statistical conceptions of interaction and instead encourages embrace of a “causal-mechanical” view of developmental relations, wherein “all phenotypes are, in fact, caused by physical interactions between genes and their environments” [Moore, this issue, p. 74]. However, emphasizing the necessity of both genetic and nongenetic factors in the construction of any phenotypic outcome does not, in itself, free epigenetics from the reductionist snares of “weak” approaches to developmental relations. As Lerner and Overton [this issue] emphasize, transcending the kind of reductionism that keeps the nature-nurture debate alive requires the field to explicitly frame the *source* of all emergent, phenotypic form in terms of *systems of relations*, that is, in terms of the constructive activity of the developmental process itself and not in terms of the components, informational or otherwise.

Thus far, epigenetics as a discipline has remained agnostic to this conceptual issue. Within the epigenetics literature, in fact, it is common to speak of one factor in a relationship as housing the “potential,” or information, for the construction of a phenotype and of another factor as “triggering” or “decoding” that potential – as the means by which that potential is actualized or expressed. In other words, epigenetics as a discipline has yet to dispel the notion that traits, by means of “information” for their construction, essentially preexist the processes involved in their development. What the proponents of epigenetics *have* explicitly done is extend talk of “potential” and “information” to the environment outside the genome, such that extragenetic factors can serve alongside genetic factors as sources of information for the construction of phenotypic form. But this in itself does nothing to discourage the idea that

components within a system of relations can, in and of themselves, serve as sources of emergent phenotypes via the information they carry.

Such a “component as source” notion of how phenotypic outcomes emerge through developmental process is at odds with a holistic view of developmental relations – with a “strong” [Overton, 1973] or “developmental systems” [Lerner, 2002; Oyama, 1985; Spencer et al., 2009] approach. Granted, epigenetic research itself is perfectly compatible with both a “strong” and a “weak” conceptualization of developmental relations. But this is precisely why the research, *by itself*, cannot adjudicate the nature-nurture debate. For every example of epigenetic research being framed in terms of strong developmental relations, one or more examples of weak framing are readily available. Consider, for example, the language routinely employed in the epigenetics literature – language which, as Lerner and Overton [this issue] importantly argue, “is not ‘innocent,’ that is, free of implicit theoretical assumptions” (p. 110).

Proponents of epigenetics research largely adhere [though not without criticism, e.g., Gonzalez-Pardo & Alvarez, 2013] to algorithmic/computational terminology, a practice that is consistent with tradition in molecular biology but that also actively encourages mechanistic decomposition of developmental relations. Talk of information in genomes being “silenced” or “expressed” by the activity of extragenetic factors is commonplace in the epigenetics literature. Environmental factors are routinely discussed as “signals” that activate genetic information. Noncoding DNA and RNA are described as helping to “translate, with the active help of instructive environmental signals, sequential information encoded in the genome” [Stotz, 2008, p. 363]. Epigenetic factors “transmit to different cell lineages different ‘interpretations’ of DNA information” [Meloni, 2014, p. 3]. Such information theory talk often extends to extragenetic as well as genetic factors. However, the idea of *individual factors* as informational sources for phenotypic form, *rather than the relations among factors*, remains largely unchallenged in the literature, buttressed by the language employed. For example, in their influential review of epigenetic regulation and “how the genome integrates intrinsic and environmental signals,” Jaenisch and Bird [2003] write:

The genetic information of an organism is differentially expressed in both time and space through mechanisms that we are finally beginning to understand. Epigenetic mechanisms constrain expression by adapting regions of the genome to maintain either gene silencing or gene activity. (p. 251)

In their recent conceptualization of epigenetics, the philosophers Griffiths and Stotz [Griffiths & Stotz, 2013; Stotz & Griffiths, 2016] appeal to the distinction (originally from embryology [Holtzer, 1968]) between *instructive* and *permissive* factors in characterizing different roles and contributions of components in any given developmental process. Importantly, they clearly argue that both genes *and* extragenetic factors can fulfill either an instructive or permissive role, depending on the nature of the specific relations involved. But the very idea of deconstructing developmental relations into instructive and permissive partners – and applying such a demarcation when trying to capture the dynamics of the relations – ultimately de-emphasizes the relations themselves and instead calls attention to the components that comprise the relations, as if the components themselves were the sources of developmental form. When discussing the specificity of a developmental outcome, Griffiths and Stotz [2013] admirably argue for a distributed model of causality; as they suggest, “specificity turns out to be not inherent in any single biomolecule in these networks but in-

duced by regulated recruitment and combinatorial control” such that “sequence specificity ... is distributed between a myriad of factors other than the original coding sequence” [Stotz & Griffiths, 2016, p. 6]. However, they also propose that genetic and extragenetic factors “are alternative sources of sequence information” [Griffiths & Stotz, 2013, p. 99]. Under these circumstances, their argument for specificity of the developmental product as distributed seems to imply that different factors – both genetic and extragenetic – in different contexts of relation can be sources of specificity. Stotz and Griffiths thus promote a weak developmental relations view of components (in relation to one another) as sources of specificity (sometimes the genes specify, sometimes extragenetic factors specify), rather than appealing to the relational activity itself as the source of specificity.

Simply put, the consequences of epigenetic processes cannot be predicted from the properties of the components that stand in relation to one another. What genes contribute to development depends on when and where they are activated, and this depends on factors well above the level of the gene. Epigenetic processes are emergent properties of historical and situated relations across multiple levels of biological organization. This inclusive perspective on epigenetics provides a framework to describe and analyze dynamic processes at many levels of organization, without an implicit bias about what factors/parts of the system are driving or controlling the process. We term this approach *developmental epigenetics*.

Developmental Epigenetics

Our argument for a developmental epigenetics emphasizes that the relevant context or reference for all explanations of developmental outcome is the dynamical and relational properties of developing systems, not just the properties at play at the molecular (genetic) level of analysis (or any other level of analysis for that matter). The psychobiologist Howard Moltz [1965] summarized this distributed view of developmental causality more than 50 years ago in language that was remarkably predictive of our current knowledge of the dynamics of the developmental process:

An epigenetic approach holds that all response systems are synthesized during ontogeny and that this synthesis involves the integrative influence of both intraorganic processes and extrinsic stimulative conditions. It considers the gene effects to be contingent on environmental conditions and regards the genotype as capable of entering into different classes of relationships depending on the prevailing environmental context. In the epigeneticist's view, the environment is not benignly supportive, but actively implicated in determining the very structure and organization of each response system. (p. 44)

Lerner and Overton [this issue] extend and further articulate the developmental epigenetic approach. They write:

The burgeoning and convincing literature of epigenetics means that genetic function is a relatively plastic outcome of mutually influential relations among genes and the multiple levels of the context within which they are embedded (cellular and extracellular physiological processes, psychological functioning, and the physical, social, and cultural features of the changing ecology). (p. 117)

The various demonstrations of bidirectional traffic among intra- and extra-organismic components of individual-system relations reviewed in the articles of this special issue highlight the fact that environmental and genetic influences are always coactors in the developmental process and change. Advances in the life sciences have made it clear that in addition to their genes, organisms inherit a wealth of developmental resources; this typically includes a stimulative environment containing parents, peers, as well as the varied provisions of their ecological and social niche. These features of the developmental ecology can extend across generations and contribute to both the stability *and* the variation in phenotypic outcomes that researchers in biology and psychology seek to understand. The developmentalist Susan Oyama [1989] outlined this expanded “systems” perspective on the transmission of developmental resources between generations, including (a) genes, (b) the cellular machinery necessary for their functioning, (c) the extracellular environment, and (d) the larger context, which can include the maternal reproductive system, parental care or relations with other conspecifics, as well as other aspects of the animate and inanimate world. This systems perspective moves us away from viewing genes as privileged sources of encapsulated information for development, a view all too commonplace in many current accounts of epigenetics.

But toppling genes from a position of privilege in our explanatory accounts does little, in itself, to advance a *developmental* epigenetics and its concomitant systems perspective. To render epigenetics truly developmental, what needs to be toppled is the idea that *any* component of a system is a privileged informational source of new levels of phenotypic organization in development, relative to any other component of a system, *under any circumstance*. Using the well-worn H₂O example of emergence and parity, “information” for water no more exists in hydrogen than in oxygen. In fact, it simply does not make sense to talk about “information” (privileged or otherwise) for water existing in *either* of its atomic constituents, given that both hydrogen and oxygen existed in this universe before water ever did. Clearly, the *wetness* of water is not prefigured in either of its atomic constituents. Both hydrogen and oxygen, as separate chemical elements, are associated with fire and burning, not with wetness; hydrogen itself is combustible – it burns – and oxygen supports/facilitates burning. However, the emergent product of their particular relational union, H₂O, undermines burning. Neither hydrogen nor oxygen is more causally primary to the emergent organization of water, and neither element can be sensibly assigned an “instructional” or a merely “permissive” role in the relational complex of H₂O. Although water emerges from the specific covalent bond between *two* hydrogen atoms and *one* oxygen atom, this does not make hydrogen more of a “driving force” behind the construction of water; after all, adding another hydrogen atom to the mix does not yield more water.

As Saunders [this issue] highlights, lessons from emergence in the realm of the inorganic readily inform our understanding of developmental construction in the realm of the organic. All emergent phenotypic organization, from a systems perspective, is necessarily *irreducible* to the components whose complex, nonlinear relations produce said organization in the first place. No system component – no part of the system – drives or serves as an informational source for the system as a whole, either in its maintenance or its developmental reorganization. In fact, the very assignment of privileging to parts – treating some components of a system as more important than other components in phenotypic emergence – simply reinforces the antidevel-

opment notion that phenotypic form “can preexist the processes that give rise to it” by means of some kind of “information” available in one or multiple components that antecede its developmental construction *through relational activity* [Oyama, 1985, p. 13].

Like the other authors of this special issue, we propose that the epigenetic revolution currently under way in the biological sciences holds the potential to bring about a significant reorientation in how we attribute *cause* in the study of the process of development. In a truly developmental epigenetics, the dynamics of developmental processes entail reciprocal coactions among a system’s components such that the identity of each component depends on its relation to other components, i.e., component parts are *internally* related to one another [Kitchener, 1982; Lerner, 1978]. In effect, this is what it means for relations in a system to be *nonlinear*. Given that relations among parts of a system involve simultaneous influence among these components – because component A is affecting, while simultaneously being affected by, component B, and vice versa [Ford & Lerner, 1992] – influence is interdependently spread across all of the parts that make up the whole such that each part factors critically into the emergence of the whole without leading, guiding, prefiguring, supervising, or in any way driving the construction of the whole. As Oyama [2000] has argued, in development “there is no central organizer, no repository of goals or instructions, no prime mover” (p. S341).

What, then, “drives” the system to new levels of organization? The relational activity of the system itself – changes in the dynamics of the complex relations that comprise the system as a whole. Certainly, the activity of any given component within a system of relations may prove instrumental in destabilizing that system; in essence, this component’s activity serves as the metaphorical straw that breaks the camel’s back, rendering the system unstable, leading to a dramatic increase in the degrees of freedom within which components of the system can interrelate, and thereby opening the system to new possibilities for system organization. But any new regime of organizational stability – any new network of system relations – that developmentally emerges from such a destabilization is always a function of the actual temporal dynamics that characterize parts of a system coacting in new ways. In brief, the “cause” or source of a system’s developing organization is always the system itself – namely, the complex web of dynamic coactivity among the parts that comprise the system as a whole.

In espousing this system’s reformulation of cause in phenotypic development, we, like Oyama [2000], are not suggesting that a system’s heterogeneous parts are homogeneous. Notions of parity in the attribution of cause are not a repudiation of the distinct activities that different parts of a system engage in. Neither are parity notions a repudiation of the differential relevance of certain parts of a developing system over others to the causal story at hand. Yes, for any given emergent property of a system, some parts in the complex network of part-to-part relations that comprise the system are more *relevant* than others to an understanding of that property. But differential relevance does not imply differential influence. Differential relevance, in other words, does not mean that some parts of a system are more causally effectual – in the ontological sense of holding more power over how the system changes – than other parts.

Notions of differential influence are paradigmatically instantiated in Waters’ [2007] discussion of *actual difference makers* in casual relations. For Waters (and many others), those parts of a system whose variability (across individual systems or

across time within an individual system) accounts for greater variance (relative to other parts) in a population of outcomes constitute *casual factors that actually make a difference* in outcome. As actual difference makers, these factors are regarded as more causally efficacious to the outcome [see Tabery, 2014, for extended discussion]. We, however, have argued that a focus on differential influence critically undermines relational activity as the source of emergent organization. Parts of a system, themselves, are never causes in their own right – emergence always involves a relationship among parts, and no part of a relationship holds greater or more important *formative status* relative to any other part [Gottlieb, 1992; Thelen & Smith, 1994]. At any given point in time, certain subsystems of relations are more relevant than others for understanding an emergent phenomenon in the system as a whole, not because of the variance they account for in a population but because of their position in the organized hierarchy of system relations.

At any given point in their development, complex systems, by definition, involve multiple levels of heterogeneous organization. The developing human fetus, for example, consists of organs, each of which is comprised of tissues, which themselves are made up of cells that contain various chemical constituents, including genetic material. These multiple levels of organization are *hierarchically structured* such that organs, as wholes, coact with other organs, *qua* organs, and such coactivity at the level of organ-organ relations is irreducible to the constituent coactivities of the individual tissues that comprise the organs (since organs are characterized by emergent properties not evident at the level of the tissues that comprise them). Critically, this means that the activity of any given component of the complex system under question is *local* to the immediate level of system structure to which the component belongs. Gene activity, for example, is specific to the local context of the cell [Johnston & Edwards, 2002]. Similarly, methylation as a process is specific to the local context of the cell. As components of any system act locally, so the significance of their activity should be defined locally.

Thus, which components of a system are deemed most relevant to understanding that system depends on what level of system organization is under investigation. If our interest is in the functioning of a particular organ within the human body, for example, those components of the organism *most relevant* to our line of investigation would be other proximal organs of the body, as well as the level of organization immediately below the organ – namely, the tissues that comprise it. In other words, establishing scientifically viable and manageable networks of relations to examine in order to explain development involves first defining the level of organization for the phenomenon to be explained and then investigating those system factors most immediately proximal – spatially and in terms of level of organization – to the phenomenon. Lehrman [1953] invoked precisely this principle when he famously argued that genes do not interact with environments, only organisms do. Skipping across levels of organization, as in directly relating methylation processes to organismic behavior/activity, is wholly inconsistent with an understanding of process to the extent that it encourages both an ignorance and likely dismissal of the necessary chain of local activities involved [Michel & Moore, 1995]. Skipping levels also readily invokes the notion of “information transmission” to explain the workings of complex networks of local activities, as when brain activity is related to the movement of one’s arm through appeal to the “information” or set of “instructions” for arm raising that is carried across numerous chains of local activity from brain to arm, with the local activities themselves simply carrying out orders from above.

The notion that processes (both synchronic and diachronic) are always local grounds an understanding of phenotypic development in terms of relations and activity – local activities in relation to other local activities, constituting a hierarchically organized network of local relations that gives rise to emergent organization in the system [see Witherington & Lickliter, 2016, for additional discussion]. Such a conceptual framing also makes the truly developmental study of epigenetics manageable by establishing structural grounds for determining what factors of complex systems are most relevant to the task at hand.

Concluding Thoughts

Epigenetics plays an increasingly prominent role in our understanding of development, heredity, and evolution. The literature on epigenetics is growing at an unprecedented rate, and the impact of epigenetic research on theory and practice in biology, psychology, sociology, and medicine is only beginning to be felt. The insight that a wide range of factors both internal and external to the individual organism are key participants in gene activity and differential activation represents a dramatic shift in thinking from 20th century biological dogma. In particular, widely held assumptions regarding the role of genes in development, heredity, and evolution (including that the instructions for building organisms reside in their genes, genes are the exclusive means by which these instructions are transmitted from one generation to the next, and that there is no meaningful feedback from the experience of the organism to its genes) have been shown to be false and in need of revision. Our primary concern in this special issue has been to examine the *conceptual* potential of epigenetics for resolving and transcending the enduring nature-nurture debate. Specifically, we asked “are we there yet?” It seems the answer to this question, at least at present, is “not yet.” We propose that a truly developmental epigenetics is, however, up to the task. This approach emphasizes that epigenetic processes are emergent properties of historical and situated relations across multiple levels of biological organization. Postgenomic biology and psychology are both being led to embrace this systems-oriented view of development, one that acknowledges and addresses the importance of emergence, context, and hierarchical relations in all developmental explanation.

In deepening our appreciation of the complex array of developmental resources, hidden regulators, and experiential nuances at play in the process of human development, developmental epigenetics can provide a platform for a truly situated, embodied, and relational psychobiological systems theory. As Robert, Hall, and Olson [2001, p. 959] proposed more than a decade ago: “Epigenetics is the practice of what developmental systems theory proposes.” Whether this practice effectively leads to the systems-level view of development necessary to conceptually transcend the worn and outdated nature-nurture controversy remains to be seen.

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