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The transformative role of epigenetics in child development research:
Commentary on the Special Section

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Abstract

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Lester, Conradt, and Marsit (2016, this issue) have assembled a set of papers that bring to readers of *Child Development* the scope and impact of the exponentially growing research on epigenetics and child development. This commentary aims to place this work in a broader context of theory and research by: (1) providing a conceptual framework for developmental scientists who may be only moderately familiar with this emergent field; (2) considering these contributions in relation to the current status of work, highlighting its transformative nature; (3) suggesting cautions to keep in mind, while simultaneously clarifying that these do not undermine important new insights; and (4) identifying the prospects for future work that builds on the progress reflected in this special section.

In our current era of hype, transformative is a word too often used when it is unwarranted. In the case of this Special Section on Epigenetics and Child Development, it is both warranted and almost inadequate. Lester, Conradt, and Marsit (2016, this issue) are to be commended both for assembling a set of papers that bring to readers of *Child Development* the scope and impact of the exponentially growing research on epigenetics and child development, and for providing a focused and accessible Introduction to the key issues in this work.

In seeking to capture the strengths of this Special Section, and the early stages of the transformation it illustrates, this commentary is organized to: (1) provide a conceptual framework for developmental scientists who may be only moderately familiar with this emergent field; (2) consider the contributions in this special section in relation to the current status of work in the field, further highlighting its transformative nature; (3) suggest some cautions that need to be kept in mind as the work moves forward, while simultaneously clarifying that these do not undermine the important new insights that this approach affords; and (4) identify the prospects and potential directions of future work that builds on the progress reflected in this special section.

Conceptual Framework

An important initial observation is that the burgeoning work on epigenetics in general; on social epigenetics, and on epigenetics and child development, strongly reinforces the recognition that genes and the environment, nature and nurture, are engaged in complex interactions and transactions, rather than acting as opposing forces (Keating, 2011). There is substantially longer research history on epigenetic modifications arising from physical exposures such as tobacco

smoking (Steenaaard, Ligthart, Stolk, Peters et al., 2015; Stroud, Papandonatos, Salisbury, Phipps et al., 2016, this issue), Bisphenol A (BPA; Nahar, Kim, Sartor & Dolinoy, 2014), and other sources. This historical trend is evident in Lester and colleagues' Figure 2 (2016, this issue). More recently, evidence has accumulated that social transactions also lead to the chemical transformation of gene expression by virtue of DNA-methylation and histone modifications. This has generated the new approach known as social epigenetics (Szyf, 2013; Szyf, McGowan, & Meaney, 2008), and within that, the specific focus on early adversity and stress as a particularly sensitive period for epigenetic activity linked to social factors has generated great interest among developmental scientists, as represented in the papers of this special section.

Along with long-standing work on synaptic pruning (e.g., Webb, Monk, & Nelson, 2001), epigenetic modifications comprise the central underlying mechanisms of the nature-nurture transaction. If we see synaptic pruning as identifying a mechanism by which the “brain listens to the environment”, then we can also see that epigenetics identifies a mechanism by which “genes listen to the environment.” In both cases, developmental experiences, especially in early life and during adolescence, and the social context in which they occur, have the capability to become biologically embedded with lifelong impacts on developmental health (Boyce & Keating, 2004; Keating & Hertzman, 1999; Kundakovic & Champagne, 2015).

The significance of identifying specific mechanisms through which this biological embedding occurs will be obvious to developmental scientists. Understanding much more precisely the developmental experiences and social contexts in which such biological embedding occurs becomes fundamental to explaining the long reach of early experience, as those transactions “get under the skin” (McEwen, 2012). A particularly salient example of both scientific and practical importance is the potential to identify the active components of early life adversity (ELA) and stress as they contribute to both immediate and lifelong social disparities in health and developmental outcomes (Boyce, Sokolowski, & Robinson, 2012; Boyce & Keating, 2004; Keating, 2009; McEwen, 2012; Monk, Spicer, & Champagne, 2012).

A second key observation is noted by Lester et al. (2016, this issue) in their Figure 2: research on epigenetics and child development is at the launching point of an exponential growth curve. If we think of each of the studies depicted there as lighting up a pixel on a large monitor, what we realize is that there is far more unknown space compared to what has been explored. Despite this, there are some patterns that have begun to emerge clearly enough that we can begin

to regard them as setting a baseline for Bayesian inference and model-building going forward (Gelman & Shalizi, 2013). This is especially true in the case of specific findings that link together epigenetic work on both animals and humans with longitudinal research on health and development at both the individual and population levels.

Several of the papers in this special section report research on one such example, the role of the gene *NR3C1* that is central to the glucocorticoid feedback loop that plays a major role in the regulation of the stress response system via the hypothalamic-pituitary-adrenal axis (Conradt, Hawes, Guerin, Armstrong et al., 2016, this issue; Kertes, Kamin, Hughes, & Rodney, 2016, this issue; Parade, Ridout, Seifer, Armstrong et al., 2016, this issue; Stroud et al., 2016, this issue). This gene has been identified as a prime candidate for lifelong impacts on health and development, owing to consistent findings regarding the role of ELA in its DNA-methylation in both animal and human research (Champagne, 2013; Kundakovic & Champagne, 2015), along with the well-established long term consequences of stress system dysregulation and allostatic load on health and developmental outcomes (McEwen, 2012).

The basic biology of DNA-methylation is well described by Lester and colleagues (2016, this issue, Figure 1), and does need to be repeated. As they note, the principal focus of work on child development and epigenetics (and much of social epigenetics more generally) has been on DNA-methylation, rather than on other epigenetic mechanisms such as histone modifications. This is partly the result of technical measurement constraints, as the technology for isolation of DNA-methylation has become more readily available. The conceptual basis is also straightforward, in that DNA-methylation operates most often in the promoter region of the gene, acting as an on-off switch, or more precisely as a dimmer switch, controlling the output of that gene. Moreover, the replication and extension of DNA-methylation research provides an increasingly valuable empirical template against which to test new candidate genes or a deeper understanding of the functioning of genes that have previously been research targets for their potential explanatory roles.

It is important to recognize that there are multiple ways to approach the assessment of DNA-methylation. The three major categories are global methylation; epigenome-wide methylation arrays; and candidate gene methylation. There are strengths and limitations of each. Global DNA-methylation can provide a valuable indicator of the overall intrauterine

environment, especially as it may be responding to systemic exposures such as lead (Goodrich, Sánchez, Dolinoy, Zhang et al., 2015).

Epigenome-wide arrays, now capable of sampling nearly 500,000 individual CpG sites (see Lester et al., 2016, this issue, Figure 1) in single assays, are valuable tools both for assessing overall differences between groups known or suspected to differ in relevant developmental or health status measures, and for generating hypotheses about specific epigenetic effects to be more precisely targeted in subsequent studies. In this special section, this approach is used effectively in two studies, one exploring a broad array (Beach, Lei, Brody, Kim et al., 2016, this issue) and the second focusing on specific cell types, lymphocytes (Naumova, Hein, Suderman, Barbot et al., 2016, this issue). Given the vast amount of data that epigenetic modeling and assays generate, there are clear statistical risks of multiple comparisons to be dealt with, described further below. Although challenging, these risks are not insurmountable.

The third approach focuses on specific candidate genes. In addition to four papers in this special section that focused on a key gene in the glucocorticoid feedback loop (*NR3C1*, cited above), there are two further examples of this in the special section. One focuses on a gene that operates in the serotonergic system (*SLC6A4*), and in this study greater DNA-methylation was associated with more difficulties of temperament at 3-months-old among preterm infants but not full term infants (Montirosso, Provenzi, Fumagalli, Sirgiovanni et al., 2016, this issue). A key finding was that *SLC6A4* methylation at a number of CpG sites was more pronounced among the premature infants following a stay in a neonatal intensive care unit, a likely significant early life stressor, compared to their methylation status at birth. Smearman, Almlı, Conneely, Brody and colleagues (2016, this issue) focused on a different candidate, *OXTR*, an oxytocin receptor gene. Although the observed direct effect of greater methylation of this gene did not survive corrections for multiple comparisons, methylation at several of its CpG sites was a significant moderator, in that childhood abuse interacted with methylation at those specific *OXTR* CpG sites to predict depression and anxiety symptoms in adulthood.

Although there is much to be learned from both global methylation studies and those using non-targeted or partially targeted methylation arrays, there is an ongoing push toward greater specificity afforded by the candidate gene approach for several reasons. Perhaps most important, it enables hypothesis generation and testing that focuses on the specific mechanism whose function is (at least partially) understood. The downstream biological effect of DNA-

methylation is the dimming, or in extreme cases, cessation of the production of proteins that are responsible for specific physiological functions. When we know the biological role that they play, such as in the diminished capacity of the glucocorticoid feedback loop to get the HPA-axis to stand down, we are in a much better position to link that mechanism to physiological, psychological, and behavioral consequences, and ultimately to impacts on lifelong health and developmental outcomes. This hypothesis testing is not only about how the gene functions, but also about the nature of the developmental experiences, such as early life adversity, that give rise to the observed consequences. It also enables testing the level and impact of biological embedding (Keating & Hertzman, 1999), especially if longitudinal data are available for both biology and behavior.

In pursuing such hypothesis generation and testing, it makes sense to ask, “What makes a good candidate gene?” Most promising are those whose biological function is known to some extent, but especially for developmental scientists, another criterion is those genes whose functions are relevant to broader constructs of social context, behavioral and psychological consequences, and lifelong impacts. The papers in this special section focusing on candidate genes draw on that larger construct space bringing biological, social, and developmental research to bear on the central questions: the HPA-axis of the stress response system (Conradt et al., 2016, this issue; Kertes et al., 2016, this issue; Parade et al., 2016, this issue; Stroud et al., 2016, this issue); the serotonergic system (Montirosi et al., 2016, this issue); and the oxytocin system (Smearman et al., 2016, this issue). In each of these cases, there is a substantial research literature from biological and developmental science identifying them as candidate genes of great potential interest, because of the connections to important developmental and health processes and outcomes.

As noted above, at this time the field of epigenetics and child development has far more blank spaces to fill in than active pixels on our metaphorical monitor. Even for those areas in which a clear pattern has begun to emerge, such as epigenetic modifications that affect the stress response system, much remains to be learned. One striking example is the differential effects of *NR3C1* methylation of the placenta versus the infant’s cord blood, clearly evident in the contrasts in Kertes and colleagues’ (2016, this issue) Figure 2: higher methylation in cord blood is associated with lower birth weights (Panel B), but higher methylation in the placenta is associated with higher birth weight (Panels C and D). In addition, higher methylation was

related to higher levels of maternal stress. The implication that methylation may be protective in placental tissue but deleterious in the infant's cord blood suggests how complex these relationships are likely to be, and also emphasizes how much remains to be discovered about the specific placental characteristics (Conradt, Fei, LaGasse, Tronick et al., 2015) that are likely to be central to understanding the wide range of epigenetic effects.

The final element of the conceptual framework to be noted is not a focus of this special section, given the nature of these studies, but is important for understanding the extent of the transformation that epigenetics is likely to have in how we think about developmental processes. In addition to the interaction of the epigenome with the physical and social environment that generates "metastable epialleles" with lasting effects on the individual, transgenerational transmission of these epigenetically modified versions of the gene has been observed (Dolinoy & Jirtle, 2008, p. 4). Although human data are unavailable on the frequencies of such transmission, which is another, virtually Lamarckian pathway of biological inheritance independent of changes to DNA (Skinner, 2015), the potential for increasing the overall burden on population developmental health (Keating, Siddiqi, & Nguyen, 2013) is likely non-trivial.

The Emerging Picture

Based on the evidence from the papers in this special section, and other previous studies (cf. review by Kundakovic & Champagne, 2015), there are important patterns that can already be identified. The first is that social adversity, particularly but not exclusively early life adversity, has a uniform negative effect on a range of developmental and health outcomes, and that observed associations with DNA-methylation follow the same pattern, whether as direct effects, mediators, or moderators. We do need to be aware of a potential file-drawer effect, because null findings may not make it into the published literature as readily as positive findings. Even with that, however, the consistency of effects and their relatively uniform direction from social adversity to methylation to problems in developmental health are noteworthy (Szyf, 2013).

Also noteworthy in this special section is variety in the types of adversity that demonstrate a linked impact on methylation and developmental health consequences, including the social gradient effect of socioeconomic status (SES); parental sensitivity, acceptance or rejection; a history of child abuse; stressors associated with NICU stays; and maternal smoking (which itself has an SES component). Undoubtedly there are other kinds of adversity not fully

represented in this sample of studies, but the sensitivity of the epigenome to multiple signals of environmental variation suggests that it is likely to be a widespread phenomenon.

A second aspect of note across the papers in this special section is the pervasiveness of the observed impacts on developmental health: neonatal neurobehavior (Stroud et al., 2016, this issue); birth weight (Kertes et al., 2016, this issue); temperament in early infancy (Montirossi et al., 2016, this issue); internalizing symptoms in early childhood (Parade et al., 2016, this issue); adolescent psychosocial adjustment (Naumova et al., 2016, this issue); self-reported health in young adulthood (Beach et al., 2016, this issue); and adult psychiatric symptomatology (Smearman et al., 2016, this issue). This joint pattern of durable impacts of social adversity and the pervasiveness of its effects is strikingly similar to the social epidemiological research literature on the social and developmental determinants of health (Keating, 2009). This is unlikely to be a coincidence. More likely is that epigenetic effects are a central mechanism by which social adversity, especially ELA, becomes biologically embedded and gets under the skin (Keating & Hertzman, 1999; McEwen, 2012; Szyf et al., 2008).

The centrality of the stress response system to many of the studies in this special section, either as a source of social adversity leading to downstream consequences, or as a site where methylation has a distinct impact, or both, is also of interest. Given the degree to which this system is evolutionarily preserved across species and shows similar methylation patterns across multiple species (Kundakovic & Champagne, 2015), it is reasonable to assume that it serves an important biological purpose. To the extent that prenatal cortisol (Reynolds, 2012) or disruptions to early nurturance yield the durable and pervasive patterns noted above, it is reasonable to speculate that these may act as a signaling system to the organism that a dangerous environment awaits, and that a hyperactive stress response may provide some beneficial protection. The reality, though, is that in contemporary human development in relatively more peaceful environments this hyperactivity and the excess of cortisol it produces as a function of stress system dysregulation and lifelong allostatic load is more likely a problem than a benefit (McEwen, 2012; Reynolds, 2012). In less settled social circumstances, it may continue to serve a protective function, though likely at a cost to those who survive beyond those external risks.

One final pattern that characterizes this emergent picture of the role of epigenetics and child development is that the research, as evidenced in the papers in this special section, is deeply interdisciplinary. It is hard to imagine how such research can proceed in any other way.

Developing research mechanisms for funding and training that support this model of research and extend it beyond the pioneers of this early wave of research, will likely prove essential to scientific progress.

Cautions, But No Red Flags

As is true of any emerging research field, there are a number of methodological and analytic concerns and cautions that can be identified, and this field is no exception. At the same time, these need to be understood relative to the early stages of research in this field. A detailed critique of possible concerns is not appropriate here, but several should be noted because they are sometimes raised as major obstacles, or because the conceptual bases for the concerns are frequently not clearly articulated.

One issue has to do with what tissue types are assayed, because different cell types will be differentially methylated. Because many of the effects of interest entail neural functioning, neural cells are typically viewed as the ideal cell type. But in human studies, these will rarely be available. In some cases, differences between cell types are meaningful, as in the tissue specific effects described above between placental tissue and neonatal cord blood (Kertes et al., 2016, this issue). In other cases, it depends much more on availability rather than research focus, and can include venous blood, dried bloodspots, and buccal cells (e.g., Essex, Boyce, Hertzman, Lam et al., 2013). The degree of meaningful overlap in methylation patterns among varying cell types is not fully established, but there is substantial non-overlap. A key question is whether such variability leads to errors or confounds. Although alpha error, reporting a finding that is not actually significant, is possible, this is countered to some extent in many cases by the Bayesian expectations arising from past research (Gelman & Shalizi, 2013). The more likely probability is a tendency toward beta error, failing to detect a meaningful methylation pattern, because the signal overlap between the cell types is muted. As research proceeds, it is highly probable that many of these concerns will be addressed empirically.

Somewhat related to this is the question of effect size. Are the observed epigenetic effects of sufficient magnitude to be important in a practical sense? A key distinction here is whether the question is about relative risk or attributable risk. Relative risk concerns the additional probability of a known exposure having an effect of a specific magnitude. This is somewhat easier to estimate for a well-calibrated exposures, like maternal smoking (Stroud et al., 2016, this issue), but harder in the case a more generic exposure, like early adversity associated

with SES. The estimates of attributable risk address a different question. For example, how much stress dysregulation in the population is due to *NR3C1* methylation compared to other sources like genetic variability or overall level of stress in the society. To address this question, we would need to have population estimates that are not currently available. On the other hand, where effects are obtained whose downstream consequences across multiple studies indicate substantial convergence and pervasiveness, we can infer that the attributable risk is far from trivial. Another analytic method is to estimate the level of mediation through a methylation pathway, although that is not the only route through which effects can occur.

As noted above, the analytic approaches to correction due to multiple comparisons will continue to be a major focus, and the papers in this special section describe a range of options to address this concern. It is particularly challenging given the vast amounts of data that can be generated in considering multiple CpG sites on an epigenome-wide basis. Similar to the contrast of alpha versus beta error in dealing with multiple cell types, there is potential here for both overcorrection and undercorrection. Again, however, consistency of patterns and replicability serve as valuable constraints on interpretation and protection against uncontrolled fishing expeditions.

Future Prospects

In looking at the larger picture of how epigenetics will transform child development both conceptually and empirically, it is clear that the papers in this volume point to important directions for future research. It is certainly true that there is much more unknown than known at this point, and much of the picture remains to be filled in, but some patterns are already becoming sharper, as noted above. The easily predictable future exponential growth of this research will begin to sharpen it even further. Some of the specific research directions illustrated or implied by the research in this special section include more expansive longitudinal designs, interactions between and among epigenetic influences, more precise phenotyping of both social context and behavior, considering a broader array of the epigenome, and the interactions of genetic and epigenetic processes.

The expansion of longitudinal designs needs to focus on several aspects, and can draw on multiple approaches to do so. First, adding epigenetic information to existing longitudinal studies, as in several studies in this special section, builds on the value of already well-characterized samples. Supplemental studies that can collect biospecimens for this purpose can

make significant contributions, as evidenced in several studies in this special section. Even when that information is not prospective or even contemporaneous, it is clear that meaningful patterns can emerge. Of course, if epigenetic information can be derived from previously collected biospecimens that place them in closer temporal proximity to developmentally sensitive periods captured in the existing longitudinal data, the more precise the estimates of epigenetic effects will be. One promising avenue lies in the use of dried blood spots, collected at birth, that in some states have been maintained for research purposes. Recent technological developments have demonstrated effective extraction of DNA-methylation profiles from these newborn dried blood spots (Sen, Heredia, Senut, Hess, et al., 2015). In these cases, a post hoc prospective design becomes feasible. In all of these cases, as noted above, broad interdisciplinary teams offer the greatest promise. Developmental scientists should become key participants in such efforts, to ensure the core questions they bring to the investigation are well represented.

Another line of research that merits attention is the joint consideration of multiple epigenetic effects that may reinforce the developmental impact, such as the various ways in which early life adversity affects both methylation and developmental health. More precise longitudinal designs will also be of value here, allowing the consideration of changes in developmental trajectories, compensating or buffering effects, mitigating effects, and others. This picture will undoubtedly grow more complex rapidly.

In parallel with greater precision in the timing and range of epigenetic effects, more precise phenotyping of both context and development will grow in importance. For example, the type of adversity may matter, such as in the differential impact of chronic stress versus war time trauma observed in the study by Kertes and colleagues (2016, this issue). Greater precision at the upstream end will help to clarify the specific mechanisms in play, both epigenetic and developmental.

As the field moves forward, several additional growth points can be identified for special attention. The first is expanding the extent of the epigenome under investigation. This is a daunting prospect given the magnitude of possible effects, but collaborative work across groups, such as in the NIH Roadmap Epigenomics Mapping Consortium, will serve to accelerate this process. A second area of great interest will be interactions between genome and epigenome, especially in the study of differential vulnerability to epigenetic effects (Barr & Misener, 2015).

The research prospects for this emerging field are virtually unlimited, and the science will clearly transform how we view the central processes and outcomes of child development. It has been some time since the field moved beyond a theoretical battleground of nature versus nurture (Keating, 2011), and this emerging work both consolidates and advances theoretical approaches that move that recognition on to center stage. We now have the capability to identify the specific molecular mechanisms, both in synaptic pruning and in epigenetic modification, that afford a much richer perspective on theories about child development. In addition, it provides an important grounding for and constraints on theory. Theories about developmental processes that do not take account of the known mechanisms of how social context and developmental processes get under the skin and exert lifelong impacts will give way to those that incorporate these underlying mechanisms.

It is to be hoped that it will also transform approaches to intervention, prevention and policy. As we begin to see increasingly clearly how early life and later social adversity become biologically embedded through epigenetic mechanisms, the societal and population costs of failing to address remediable features of that adversity will become ever more apparent (Keating, 2016, in press). The additional impact from the potential transgenerational transmission of those acquired biological risks will also become clearer with further research. Social policy choices and targets of intervention are likely to be seen as more crucial than ever, but at the same time, the ability to understand the underlying mechanisms may well lead to more precisely crafted and effective approaches.

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